(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 266 922 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **87308976.7**

(22) Date of filing: **09.10.87**

(51) Int. Cl.⁴: **C07D 211/90** , C07D 401/12 , A61K 31/44 , //C07D205/04,C07D211/46,C07-D207/12

(30) Priority: **09.10.86 JP 240254/86**

(43) Date of publication of application: **11.05.88 Bulletin 88/19**

(84) Designated Contracting States: **AT BE CH DE ES FR GB GR IT LI LU NL SE**

(71) Applicant: **Sankyo Company Limited**
5-1 Nihonbashi Honcho 3-chome Chuo-ku
Tokyo(JP)

Applicant: **UBE INDUSTRIES LIMITED**
12-32, 1-chome, Nishihoncho
Ube-shi, Yamaguchi-ken(JP)

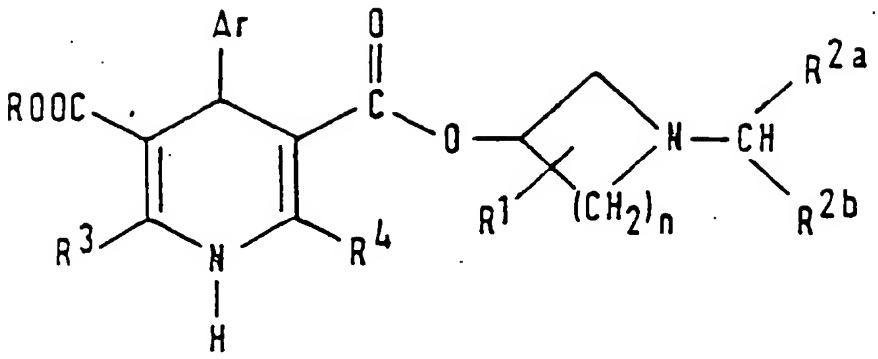
(72) Inventor: **Koike, Hiroyuki Sankyo Company Ltd.**
2-58, 1-chome, Hiromachi Shinagawa-ku
Tokyo 140(JP)
Inventor: **Yoshimoto, Masafumi Sankyo Company Ltd.**
2-58, 1-chome, Hiromachi Shinagawa-ku
Tokyo 140(JP)
Inventor: **Nishino, Hiroshi Sankyo Company Ltd.**
2-58, 1-chome, Hiromachi Shinagawa-ku
Tokyo 140(JP)

(74) Representative: **Tubby, David George**
MARKS & CLERK 57-60 Lincoln's Inn Fields
London WC2A 3LS(GB)

(54) Dihydropyridine derivatives, their preparation and their use.

(57) Compounds of formula (I):

EP 0 266 922 A1



(I)

in which:

Ar represents a phenyl group having at least one substituent selected from nitro, C_1 -C_4 haloalkyl, C_1 -C_4 haloalkoxy and cyano groups and halogen atoms;

R represents a C_1 -C_{16} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_4 alkyl group having a C_3 -C_6 cycloalkyl substituent, a C_2 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{16} alkyl group having at least one substituent selected from hydroxy, C_1 -C_4 alkoxy and C_1 -C_4 alkylthio groups;

R^1 represents a hydrogen atom or a C_1 -C_3 alkyl group;

R^{2a} and R^{2b} are the same or different and each represents an unsubstituted phenyl group or a substituted phenyl group having at least one substituent selected from C_1 -C_4 alkyl, C_1 -C_4 alkoxy and C_1 -C_4 haloalkyl groups and halogen atoms;

one of R^3 and R^4 represents a methyl group and the other represents an amino group; and

n is an integer from 1 to 3;

These compounds have a variety of valuable activities, including antihypertensive and Ca^{++}-blocking activities, leading to their use for the treatment of circulatory and coronary disorders. They may be prepared by condensation of appropriate substituted benzylideneacetoacetic acid esters with appropriate amidinoacetic acid esters.

DIHYDROPYRIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE

The present invention relates to a series of new dihydropyridine derivatives, and provides a process for preparing them as well as compositions for their pharmaceutical use.

Circulatory and coronary disorders are amongst the major causes of death in the industrialized world and, even where they do not result in death, some disablement or a severe curtailment of lifestyle may result. Notwithstanding this, the full etiology of such disorders has not been resolved, even though certain factors, notably genetic and dietary factors, have been implicated. There is, therefore, a substantial need for medicines to treat this major problem. In attempting to treat circulatory and coronary disorders, attention has been focused on a variety of different pharmacodynamic activities, and the drugs used in such treatment have a variety of different structures, depending upon the particular pharmacodynamic activity which it is desired to influence.

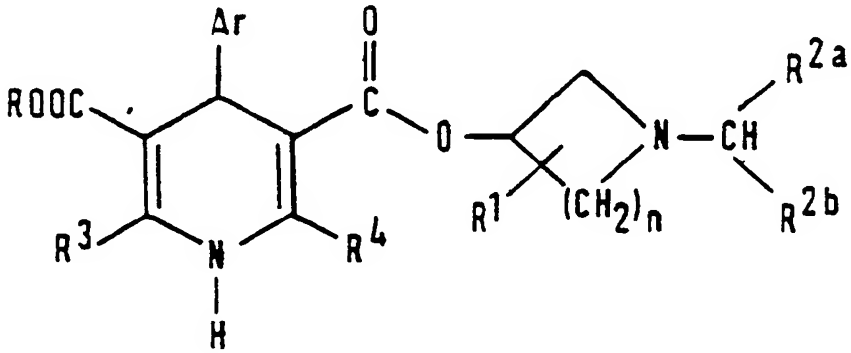
Of the many classes of drug proposed for use in such treatment, some compounds have a 4-(substituted phenyl)-1,4-dihydropyridine basic structure and included within such general classes of drug are nifedipine (which is included amongst the compounds disclosed in British Patent Specification No. 1 173 862) and nicardipine (which is included amongst the compounds disclosed in British Patent Specification No. 1 455 502). All of these compounds have in common a 4-(nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid ester structure.

However, it is believed that the closest prior art to the compounds of the present invention is disclosed in Arzneim. - Forsh., 31, 1173 (1981) and in European Patent Publication No. 125 803. Both of these disclose compounds which are said to have cardiovascular activity, in much the same way as do the compounds of the present invention. However, the compounds of the former prior art differ from those of the present invention in the nature of the ester grouping at the 1,4-dihydropyridine system. The latter prior art, although disclosing compounds some of which have an ester grouping resembling that of the present invention, differ in the overall structure of the compounds and notably in the nature of the groups at the 2- and 6-positions of the dihydropyridine ring.

Other related compounds are disclosed in European Patent Publication No. 207 674, but these differ from the compounds of the present invention in that the prior compounds contain a nitrooxy group in their molecular structure, which is not possesed by the compounds of the present invention.

We have now discovered a series of novel dihydropyridine derivatives having excellent calcium-blocking activity, as well as antihypertensive, antihyperlipemic and vasodilator activities and the ability to inhibit the formation of lipid peroxides.

The compounds of the invention are those dihydropyridine derivatives of formula (I):



(I)

in which:

Ar represents a phenyl group having at least one substituent selected from nitro, C_1 -C_4 haloalkyl, C_1 -C_4 haloalkoxy and cyano groups and halogen atoms;

R represents a C_1 -C_{16} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_4 alkyl group having a C_3 -C_6 cycloalkyl substituent, a C_2 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{16} alkyl group having at least one substituent selected from hydroxy, C_1 -C_4 alkoxy and C_1 -C_4 alkylthio groups;

R^1 represents a hydrogen atom or a C_1 -C_3 alkyl group (and may be a substituent on any of the carbon atoms of the nitrogen-containing heterocyclic group);

R^{2a} and R^{2b} are the same or different and each represents an unsubstituted phenyl group or a substituted phenyl group having at least one substituent selected from C_1 -C_4 alkyl, C_1 -C_4 alkoxy and C_1 -C_4 haloalkyl groups and halogen atoms;

one of R^3 and R^4 represents a methyl group and the other represents an amino group; and

n is an integer from 1 to 3;

and pharmaceutically acceptable acid addition salts thereof.

The invention also provides a pharmaceutical composition for the treatment of cardiovascular disorders, which composition comprises a dihydropyridine derivative in admixture with a pharmaceutically acceptable carrier or diluent, wherein said dihydropyridine derivative is at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention still further provides the use for the manufacture of a medicament, especially for the treatment of cardiovascular disorders, of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention also provides processes for preparing the compounds of the invention, which are described in more detail hereafter.

The compounds of the present invention have been found to have various valuable pharmacological activities such as calcium antagonism, antihypertensive and vasodilator activity as well as low toxicity and are thus useful as medicines for the treatment of cardiovascular dysfunctions such as hypertension and angina pectoris.

In the compounds of the invention, Ar represents a phenyl group which has at least one, and preferably only one, nitro, C_1 -C_4 haloalkyl, C_1 -C_4 haloalkoxy or cyano substituent, or at least one, and preferably one or two, halogen substituents.

In particular, we prefer that Ar should represent a phenyl group having a single substituent selected from nitro groups, haloalkyl groups containing one or two carbon atoms (such as the trifluoromethyl or 2,2,2-trifluoroethyl groups), haloalkoxy groups containing one to two carbon atoms (such as the difluoromethoxy group, trifluoromethoxy group or 2,2-difluoroethoxy group) and cyano groups. Alternatively, we prefer that Ar should represent a phenyl group containing one or two halogen atoms (such as the fluorine, chlorine, bromine or iodine atoms) as substituents. Preferred such groups represented by Ar are the o-nitrophenyl, m-nitrophenyl, p-nitrophenyl, o-chlorophenyl, m-chlorophenyl, p-chlorophenyl, o-cyanophenyl, m-cyanophenyl, o-trifluoromethylphenyl, m-trifluoromethylphenyl, o-difluoromethoxyphenyl, m-difluoromethoxyphenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl and 2,4-dichlorophenyl groups, of these, we particularly prefer the o-nitrophenyl, m-nitrophenyl, o-chlorophenyl, m-chlorophenyl and 2,3-dichlorophenyl groups.

R^1 Represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms. Examples of such groups include the methyl, ethyl, propyl and isopropyl groups. The hydrogen atom and the methyl group are preferred, and the hydrogen atom is most preferred.

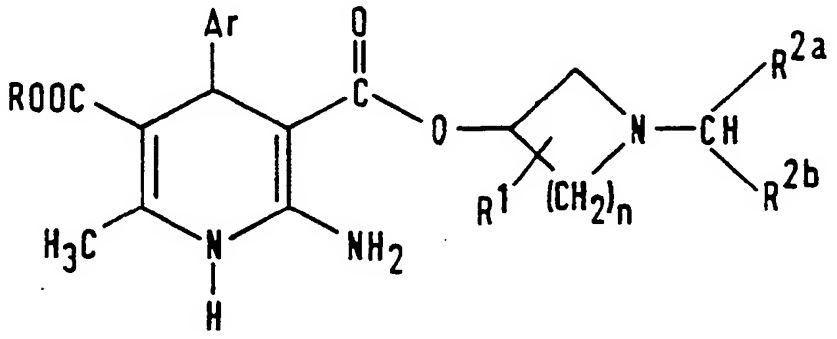
R^{2a} and R^{2b} are the same or different and each represents a phenyl group which may be unsubstituted or have at least on C_1 -C_4 alkyl, C_1 -C_4 alkoxy, C_1 -C_4 haloalkyl or halogen substituent and the two groups represented by R^{2a} and R^{2b} may be the same or different, but they are preferably the same. Where the substituent is an alkyl group, this is preferably a C_1 -C_3 alkyl group, such as a methyl, ethyl, propyl or isopropyl group. Where the substituent is an alkoxy group, this is preferably a C_1 -C_3 alkoxy group, such as a methoxy, ethoxy, propoxy or isopropoxy group. Where the substituent is a halogen atom, this is preferably a fluorine, chlorine, bromine or iodine atom. Where the substituent is a haloalkyl group, this is preferably a C_1 or C_2 haloalkyl group, such as a trifluoromethyl or 2,2,2-trifluoroethyl group, especially a trifluoromethyl group.

Where R represents a straight or branched chain alkyl group containing from one to sixteen carbon atoms, it preferably has from one to ten carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl, octyl and decyl groups. Such may be unsubstituted or may have one or more, and preferably only one substituent, as defined below.

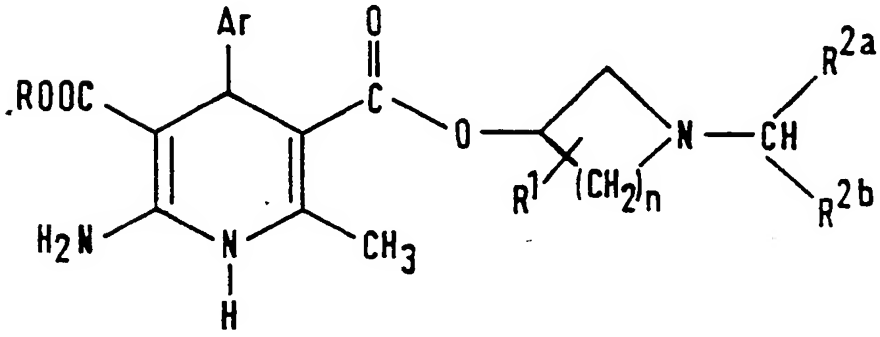
The C_1 -C_{16} alkyl groups represented by R may be unsubstituted or have at least one substituent selected from hydroxy groups, C_1 -C_4, preferably C_1 -C_3, alkoxy groups (such as the methoxy, ethoxy, propoxy or isopropoxy groups) or C_1 -C_4, preferably C_1 -C_3, alkylthio groups (such as the methylthio, ethylthio, propylthio or isopropylthio groups).

Where R represents a cycloalkyl group containing from three to six carbon atoms, it may be, for example, a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Where R represents a C_1 -C_4 alkyl group having a C_3 -C_6 cycloalkyl substituent, this is a cycloalkylalkyl group containing from four to eight carbon atoms, and examples include the cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl and 2-cyclohexylethyl groups. Where R represents a C_2 -C_4 alkyl group, it is preferable an alkenyl group containing three or four carbon atoms, for example an allyl or 2-butenyl group.

One of R^3 and R^4 represents a methyl group and the other represents an amino group; thus, the compounds of the present invention may be divided into two classes, as illustrated by formulae (Ia) and (Ib):



(Ia)



(Ib)

in which Ar, n, R, R^1, R^{2a} and R^{2b} are as defined above; in these formulae, R^{2a} and R^{2b} are preferably the same groups.

Preferred classes of compounds of the present invention are:

(1) Those compounds of formula (I) in which:

Ar represents a phenyl group having a single substituent selected from nitro, C_1 -C_2 haloalkyl, C_1 -C_2 haloalkoxy and cyano groups or having one or two halogen substituents;

R represents a C_1 -C_{10} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_2 alkyl group having a C_3 -C_6 cycloalkyl substituent, a C_3 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{10} alkyl group having at least one substituent selected from hydroxy, C_1 -C_3 alkoxy and C_1 -C_3 alkylthio groups;

R^1 represents a hydrogen atom or a C_1 -C_3 alkyl group;

R^{2a} and R^{2b} are the same or different and each represents an unsubstituted phenyl group or a substituted phenyl group having at least one substituent selected from C_1 -C_3 alkyl, C_1 -C_3 alkoxy and trifluoromethyl groups and halogen atoms;

one of R^3 and R^4 represents a methyl group and the other represents an amino group; and

n is an integer from 1 to 3;

and pharmaceutically acceptable acid addition salts thereof.

(2) Those compounds defined in (I) above in which R^{2a} and R^{2b} are the same.

(3) Those compounds defined in (I) or (2) above in which R^3 represents a methyl group and R^4 represents an amino group.

More preferred classes of compounds of the present invention are:

(4) Those compounds of formula (I) in which:

Ar represents a phenyl group having a single substituent selected from nitro, trifluoromethyl, difluoromethoxy and cyano groups or having one or two chloro substituents;

R represents a alkyl group (especially one containing from one to six carbon atoms, such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl group), an alkoxyalkyl group containing a total of from three to five carbon atoms (such as a 2-methoxyethyl, 2-ethoxyethyl or 2-propoxyethyl group), an alkylthioalkyl group containing a total of three or four carbon atoms (such as a 2-methylthioethyl, 3-methylthiopropyl or 2-ethylthioethyl group), a cycloalkyl group containing five or six carbon atoms (such as a cyclopentyl or cyclohexyl group), a cycloalkylalkyl group containing a total of from four to seven carbon atoms (such as a cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl group), an alkenyl group containing three or four carbon atoms (such as an allyl or 2-butenyl group), or a cinnamyl group;

R^1 represents a hydrogen atom or a methyl group; and

R^{2a} and R^{2b} are the same and each represents a phenyl group or a phenyl group having a single substituent selected from chlorine atoms, fluorine atoms, trifluoromethyl groups, methyl groups and methoxy groups;

and pharmaceutically acceptable acid addition salts thereof.

(5) Those compounds defined in (4) above in which R^3 represents a methyl group and R^4 represents an amino group.

The most preferred classes of compounds of the present invention are:

(6) Those compounds of formula (I) in which:

Ar represents a 2-nitrophenyl group, a 3-nitrophenyl group, a 2-trifluoromethylphenyl group, a 3-trifluoromethylphenyl group, a 2-chlorophenyl group or a 2,3-dichlorophenyl group;

R represents a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, 2-methoxyethyl, 2-ethoxyethyl, 2-propoxyethyl, 2-methylthioethyl, 3-methylthiopropyl, 2-ethylthioethyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, allyl, 2-butenyl or a cinnamyl group;

R_1 represents a hydrogen atom or a methyl group; and

R^{2a} and R^{2b} are the same and each represents a phenyl group or a p-fluorophenyl group;

and pharmaceutically acceptable acid addition salts thereof.

(7) Those compounds defined in (6) above in which R^3 represents a methyl group and R^4 represents an amino group.

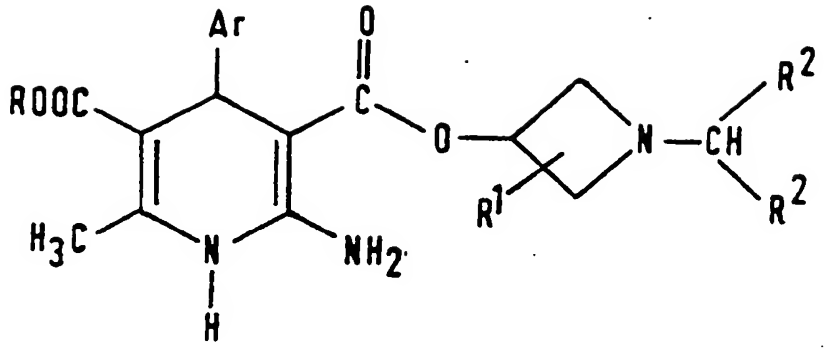
The compounds of the invention can form acid addition salts. The nature of such salts is not critical to the present invention, except that, where the salts are to be used for therapeutic purposes, they must be pharmaceutically acceptable, which as is well understood in the art, means that the salts should not have reduced activity (or unacceptably reduced activity) and should not have increased toxicity (or unacceptable increased toxicity) as compared with the free compound. However, where the salt is to be employed for other purposes, for example as an intermediate in the preparation of other compounds, even this criterion does not apply. A wide variety of acids may be employed to form such salts and representative examples of such acids include: mineral acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, metaphosphoric acid, nitric acid or sulphuric acid; organic carboxylic acids, such as acetic

acid, oxalic acid, tartaric acid, citric acid, benzoic acid, glycolic acid, gluconic acid, glucuronic acid, succinic acid, maleic acid or fumaric acid; and organic sulphonic acids, such as methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or p-toluenesulphonic acid. Such acid addition salts may be prepared by conventional methods well known to those skilled in the art.

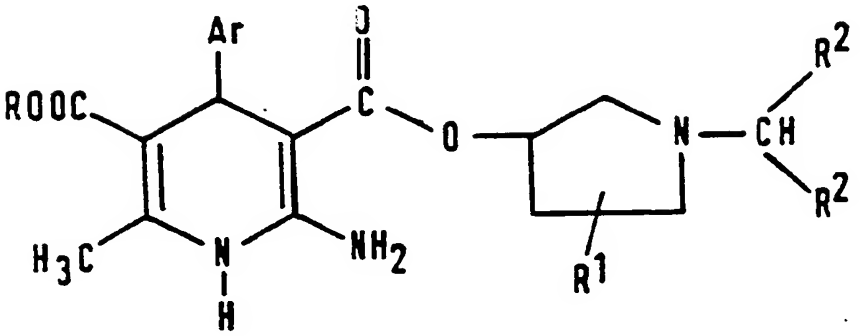
The compounds of formula (I) may contain several asymmetric carbon atoms, and thus can form a variety of optical isomers. The present invention includes both the individual isolated isomers and mixtures thereof.

Examples of specific compounds of the invention are given in the following formulae (I-1) to (I-7), in which the substituents are as defined in the corresponding one of Tables 1 to 7 [i.e. Table 1 relates to formula (I-1), Table 2 relates to formula (1-2) and so on]. The compounds of the invention are hereinafter, where appropriate, identified by the numbers appended to them in these Tables. In the Tables, the following abbreviations are used:

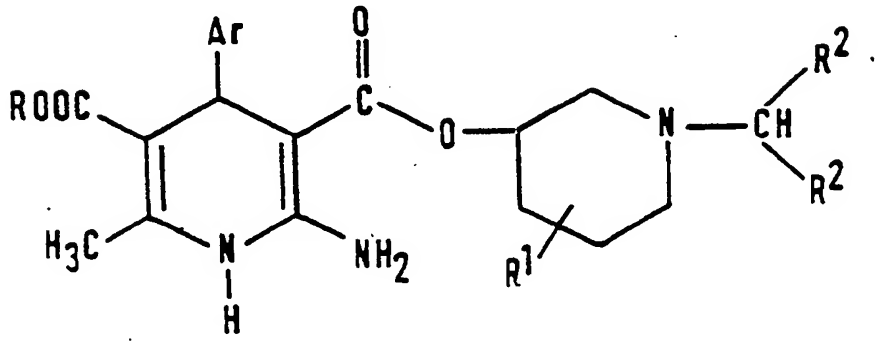
All	.....	allyl
Bu	.....	butyl
iBu	.....	isobutyl
Bun	.....	2-butenyl
Cim	.....	cinnamyl
Dc	.....	decyl
DFM	.....	difluoromethyl
Et	.....	ethyl
Hp	.....	heptyl
Hx	.....	hexyl
cHx	.....	cyclohexyl
Me	.....	methyl
Oc	.....	octyl
Ph	.....	phenyl
Pn	.....	pentyl
cPn	.....	cyclopentyl
Pr	.....	propyl
cPr	.....	cyclopropyl
iPr	.....	isopropyl
TFM	.....	trifluoromethyl



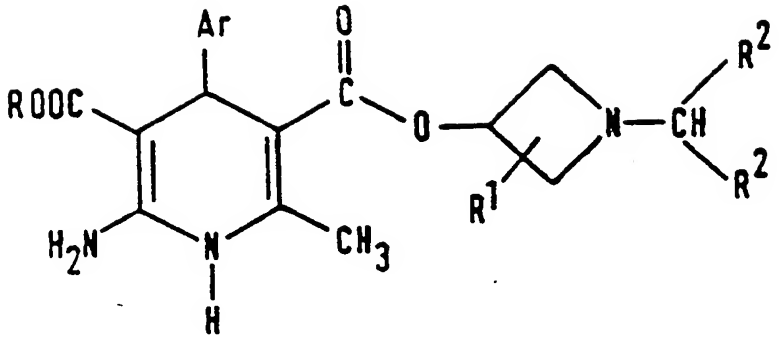
(I-1)



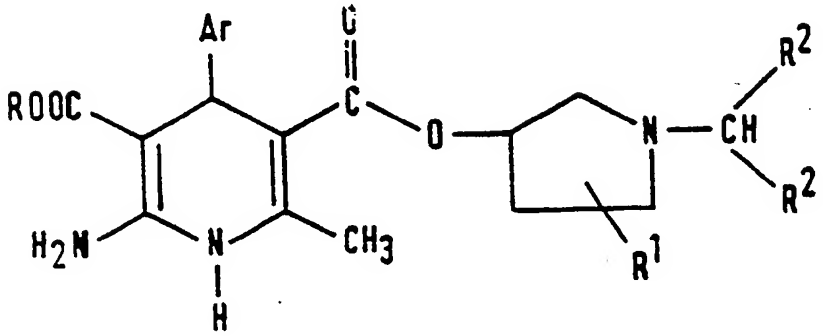
(I-2)



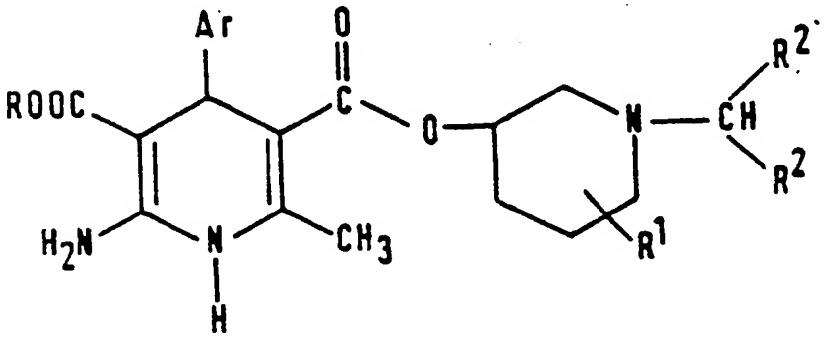
(I-3)



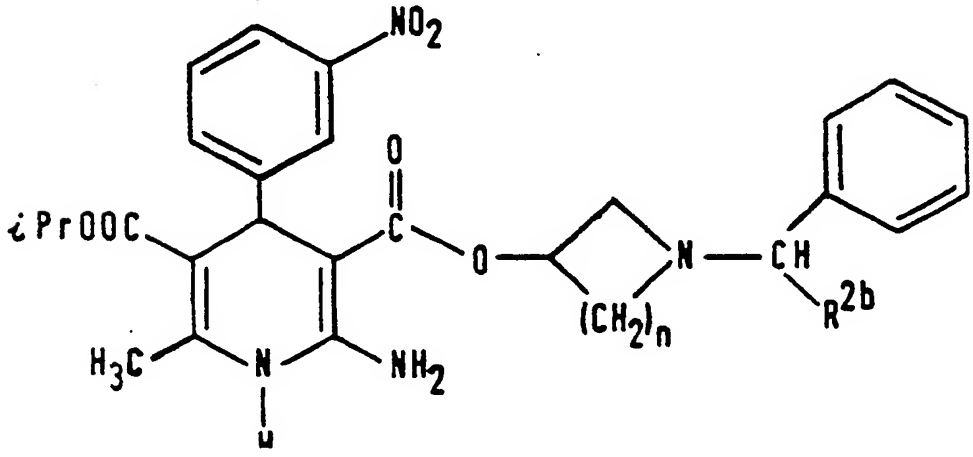
(I-4)



(I-5)



(I-6)



(I-7)

TABLE 1

Compound No.	Ar	R	R^1	R^2
1-1	o-NO_2Ph	Me	H	Ph
1-2	o-NO_2Ph	Et	H	Ph
1-3	o-NO_2Ph	iPr	H	Ph
1-4	o-NO_2Ph	Hx	H	Ph
1-5	o-NO_2Ph	2-MeOEt	H	Ph
1-6	o-NO_2Ph	cHx	H	Ph
1-7	o-NO_2Ph	Cim	H	Ph
1-8	m-NO_2Ph	Me	H	Ph
1-9	m-NO_2Ph	Et	H	Ph
1-10	m-NO_2Ph	Pr	H	Ph
1-11	m-NO_2Ph	iPr	H	Ph
1-12	m-NO_2Ph	Bu	H	Ph
1-13	m-NO_2Ph	iBu	H	Ph
1-14	m-NO_2Ph	Pn	H	Ph
1-15	m-NO_2Ph	Hx	H	Ph
1-16	m-NO_2Ph	Hp	H	Ph
1-17	m-NO_2Ph	Oc	H	Ph
1-18	m-NO_2Ph	Dc	H	Ph
1-19	m-NO_2Ph	6-HOHx	H	Ph
1-20	m-NO_2Ph	2-MeOEt	H	Ph
1-21	m-NO_2Ph	2-EtOEt	H	Ph
1-22	m-NO_2Ph	2-PrOEt	H	Ph
1-23	m-NO_2Ph	2-MeSEt	H	Ph
1-24	m-NO_2Ph	2-EtSEt	H	Ph
1-25	m-NO_2Ph	3-MeSPr	H	Ph
1-26	m-NO_2Ph	cPn	H	Ph
1-27	m-NO_2Ph	cHx	H	Ph
1-28	m-NO_2Ph	cPrMe-	H	Ph

TABLE 1 (cont)

Compound No.	Ar	R	R^1	R^2
1-29	m-NO_2Ph	cPnMe-	H	Ph
1-30	m-NO_2Ph	cHxMe-	H	Ph
1-31	m-NO_2Ph	All	H	Ph
1-32	m-NO_2Ph	Bun	H	Ph
1-33	m-NO_2Ph	Cim	H	Ph
1-34	o-TFMPh	Me	H	Ph
1-35	o-TFMPh	iPr	H	Ph
1-36	o-TFMPh	Hx	H	Ph
1-37	o-TFMPh	2-MeOEt	H	Ph
1-38	m-TFMPh	Me	H	Ph
1-39	m-TFMPh	iPr	H	Ph
1-40	m-TFMPh	Hx	H	Ph
1-41	m-TFMPh	Cim	H	Ph
1-42	o-DFMOPh	Me	H	Ph
1-43	o-DFMOPh	Et	H	Ph
1-44	o-DFMOPh	iPr	H	Ph
1-45	o-CNPh	Me	H	Ph
1-46	o-CNPh	iPr	H	Ph
1-47	o-CNPh	Hx	H	Ph
1-48	m-CNPh	Me	H	Ph
1-49	m-CNPh	iPr	H	Ph
1-50	m-CNPh	Hx	H	Ph
1-51	m-CNPh	2-MeOEt	H	Ph
1-52	o-ClPh	Me	H	Ph
1-53	o-ClPh	Et	H	Ph
1-54	o-ClPh	iPr	H	Ph
1-55	o-ClPh	Hx	H	Ph
1-56	o-ClPh	Cim	H	Ph
1-57	2,3-diClPh	Me	H	Ph

TABLE 1 (cont)

Compound No.	Ar	R	R^1	R^2
1-58	2,3-diClPh	Et	H	Ph
1-59	2,3-diClPh	iPr	H	Ph
1-60	2,3-diClPh	Hx	H	Ph
1-61	2,3-diClPh	2-MeOEt	H	Ph
1-62	2,3-diClPh	cHx	H	Ph
1-63	2,3-diClPh	All	H	Ph
1-64	2,3-diClPh	Bun	H	Ph
1-65	2,3-diClPh	Cim	H	Ph
1-66	m-NO_2Ph	Me	H	p-FPh
1-67	m-NO_2Ph	Et	H	p-FPh
1-68	m-NO_2Ph	iPr	H	p-FPh
1-69	m-NO_2Ph	Hx	H	p-FPh
1-70	m-NO_2Ph	Me	H	p-ClPh
1-71	m-NO_2Ph	iPr	H	p-ClPh
1-72	m-NO_2Ph	cHx	H	p-ClPh
1-73	m-NO_2Ph	Et	H	p-TFMPh
1-74	m-NO_2Ph	iPr	H	p-TFMPh
1-75	m-NO_2Ph	2-MeOEt	H	p-TFMPh
1-76	2,3-diClPh	iPr	H	p-FPh
1-77	m-NO_2Ph	Me	H	p-MePh
1-78	m-NO_2Ph	iPr	H	p-MeOPh
1-79	m-NO_2Ph	Hx	H	p-MeOPh
1-80	m-NO_2Ph	Me	3-Me	Ph
1-81	m-NO_2Ph	Et	3-Me	Ph
1-82	m-NO_2Ph	iPr	3-Me	Ph
1-83	m-NO_2Ph	Hx	3-Me	Ph
1-84	m-NO_2Ph	Cim	3-Me	Ph
1-85	m-NO_2Ph	iPr	3-Me	p-FPh
1-86	2,3-diClPh	iPr	3-Me	Ph

TABLE 1 (cont)

Compound No.	Ar	R	R^1	R^2
1-87	2,3-diClPh	Hx	3-Me	Ph
1-88	m-NO_2Ph	iPr	2-Me	Ph
1-89	m-NO_2Ph	Hx	2-Me	Ph
1-90	2,3-diClPh	Me	2-Me	p-FPh
1-91	2,3-diClPh	iPr	2-Me	Ph

TABLE 2

Compound No.	Ar	R	R^1	R^2
2-1	o-NO_2Ph	Me	H	Ph
2-2	o-NO_2Ph	Et	H	Ph
2-3	o-NO_2Ph	iPr	H	Ph
2-4	o-NO_2Ph	Hx	H	Ph
2-5	o-NO_2Ph	cHx	H	Ph
2-6	m-NO_2Ph	Me	H	Ph
2-7	m-NO_2Ph	Et	H	Ph
2-8	m-NO_2Ph	iPr	H	Ph
2-9	m-NO_2Ph	Hx	H	Ph
2-10	m-NO_2Ph	6-HOHx	H	Ph
2-11	m-NO_2Ph	2-MeOEt	H	Ph
2-12	m-NO_2Ph	2-MeSEt	H	Ph
2-13	m-NO_2Ph	cPn	H	Ph
2-14	m-NO_2Ph	cPrMe-	H	Ph
2-15	m-NO_2Ph	Bun	H	Ph
2-16	m-NO_2Ph	Cim	H	Ph
2-17	2,3-diClPh	Me	H	Ph
2-18	2,3-diClPh	Et	H	Ph
2-19	2,3-diClPh	iPr	H	Ph
2-20	2,3-diClPh	Hx	H	Ph
2-21	2,3-diClPh	2-MeOEt	H	Ph
2-22	2,3-diClPh	All	H	Ph
2-23	2,3-diClPh	Cim	H	Ph
2-24	m-TFMPh	Me	H	Ph
2-25	m-TFMPh	iPr	H	Ph
2-26	m-NO_2Ph	Me	H	p-FPh
2-27	m-NO_2Ph	Et	H	p-FPh
2-28	m-NO_2Ph	iPr	H	p-FPh

TABLE 2 (cont)

Compound No.	Ar	R	R^1	R^2
2-29	m-NO_2Ph	Hx	H	p-FPh
2-30	m-NO_2Ph	2-MeOEt	H	p-FPh
2-31	m-NO_2Ph	Me	H	p-ClPh
2-32	m-NO_2Ph	6-HOHx	H	p-ClPh
2-33	m-NO_2Ph	Et	H	p-MePh
2-34	m-NO_2Ph	Bun	H	p-MePh
2-35	m-NO_2Ph	iPr	H	p-TFMPh
2-36	m-NO_2Ph	Cim	H	p-TFMPh
2-37	2,3-diClPh	Me	H	p-FPh
2-38	2,3-diClPh	iPr	H	p-FPh
2-39	2,3-diClPh	Hx	H	p-FPh
2-40	m-NO_2Ph	Me	3-Me	Ph
2-41	m-NO_2Ph	iPr	3-Me	Ph
2-42	m-NO_2Ph	Hx	3-Me	Ph
2-43	m-NO_2Ph	iPr	3-Me	p-FPh
2-44	2,3-diClPh	Me	3-Me	Ph
2-45	2,3-diClPh	iPr	3-Me	Ph
2-46	m-NO_2Ph	iPr	4-Me	Ph
2-47	m-NO_2Ph	Hx	4-Me	Ph
2-48	2,3-diClPh	Me	4-Me	Ph
2-49	2,3-diClPh	iPr	4-Me	Ph

TABLE 3

Compound No.	Ar	R	R^1	R^2
3-1	o-NO_2Ph	Me	H	Ph
3-2	o-NO_2Ph	Et	H	Ph
3-3	o-NO_2Ph	iPr	H	Ph
3-4	o-NO_2Ph	Hx	H	Ph
3-5	o-NO_2Ph	cPn	H	Ph
3-6	m-NO_2Ph	Me	H	Ph
3-7	m-NO_2Ph	Et	H	Ph
3-8	m-NO_2Ph	iPr	H	Ph
3-9	m-NO_2Ph	Hx	H	Ph
3-10	m-NO_2Ph	6-HOHx	H	Ph
3-11	m-NO_2Ph	2-MeOEt	H	Ph
3-12	m-NO_2Ph	2-MeSEt	H	Ph
3-13	m-NO_2Ph	cHx	H	Ph
3-14	m-NO_2Ph	cPrMe-	H	Ph
3-15	m-NO_2Ph	All	H	Ph
3-16	m-NO_2Ph	Cim	H	Ph
3-17	2,3-diClPh	Me	H	Ph
3-18	2,3-diClPh	Et	H	Ph
3-19	2,3-diClPh	iPr	H	Ph
3-20	2,3-diClPh	Hx	H	Ph
3-21	2,3-diClPh	2-MeOEt	H	Ph
3-22	2,3-diClPh	Bun	H	Ph
3-23	2,3-diClPh	Cim	H	Ph
3-24	m-TFMPh	Me	H	Ph
3-25	m-TFMPh	iPr	H	Ph
3-26	m-CHF_2OPh	iPr	H	Ph
3-27	m-CHF_2OPh	Hx	H	Ph
3-28	m-NO_2Ph	Me	H	p-FPh

TABLE 3 (cont)

Compound No.	Ar	R	R^1	R^2
3-29	m-NO_2Ph	Et	H	p-FPh
3-30	m-NO_2Ph	iPr	H	p-FPh
3-31	m-NO_2Ph	Hx	H	p-FPh
3-32	m-NO_2Ph	Me	H	p-ClPh
3-33	m-NO_2Ph	iPr	H	p-ClPh
3-34	m-NO_2Ph	iPr	H	p-MePh
3-35	m-NO_2Ph	Hx	H	p-MePh
3-36	m-NO_2Ph	Et	H	p-TFMPh
3-37	m-NO_2Ph	iPr	H	p-TFMPh
3-38	2,3-diClPh	Me	H	p-FPh
3-39	2,3-diClPh	iPr	H	p-FPh
3-40	2,3-diClPh	Hx	H	p-FPh
3-41	m-NO_2Ph	Me	3-Me	Ph
3-42	m-NO_2Ph	Et	3-Me	Ph
3-43	m-NO_2Ph	iPr	3-Me	Ph
3-44	m-NO_2Ph	Hx	3-Me	Ph
3-45	m-NO_2Ph	Me	3-Me	p-FPh
3-46	2,3-diClPh	Me	3-Me	Ph
3-47	2,3-diClPh	iPr	3-Me	Ph
3-48	m-NO_2Ph	iPr	4-Me	Ph
3-49	m-NO_2Ph	Hx	4-Me	Ph

TABLE 4

Compound No.	Ar	R	R^1	R^2
4-1	m-NO_2Ph	Me	H	Ph
4-2	m-NO_2Ph	Et	H	Ph
4-3	m-NO_2Ph	iPr	H	Ph
4-4	m-NO_2Ph	Hx	H	Ph
4-5	m-NO_2Ph	2-MeOEt	H	Ph
4-6	m-NO_2Ph	Bun	H	Ph
4-7	m-NO_2Ph	Cim	H	Ph
4-8	m-NO_2Ph	Me	H	p-FPh
4-9	m-NO_2Ph	iPr	H	p-FPh
4-10	2,3-diClPh	Me	H	Ph
4-11	2,3-diClPh	Et	H	Ph
4-12	2,3-diClPh	iPr	H	Ph
4-13	2,3-diClPh	Hx	H	Ph
4-14	o-NO_2Ph	Me	H	Ph
4-15	o-NO_2Ph	iPr	H	Ph
4-16	m-NO_2Ph	Me	3-Me	Ph
4-17	m-NO_2Ph	iPr	3-Me	Ph

TABLE 5

Compound No.	Ar	R	R^1	R^2
5-1	m-NO_2Ph	Me	H	Ph
5-2	m-NO_2Ph	Et	H	Ph
5-3	m-NO_2Ph	iPr	H	Ph
5-4	m-NO_2Ph	Hx	H	Ph
5-5	m-NO_2Ph	All	H	Ph
5-6	m-NO_2Ph	Et	H	p-FPh
5-7	m-NO_2Ph	iPr	H	p-FPh
5-8	2,3-diClPh	Me	H	Ph
5-9	2,3-diClPh	iPr	H	Ph
5-10	2,3-diClPh	Hx	H	Ph
5-11	2,3-diClPh	5-HOPn	H	Ph
5-12	o-NO_2Ph	Et	H	Ph
5-13	o-NO_2Ph	iPr	H	Ph
5-14	m-NO_2Ph	Me	3-Me	Ph
5-15	m-NO_2Ph	iPr	4-Me	Ph

TABLE 6

Compound No.	Ar	R	R^1	R^2
6-1	m-NO_2Ph	Me	H	Ph
6-2	m-NO_2Ph	Et	H	Ph
6-3	m-NO_2Ph	iPr	H	Ph
6-4	m-NO_2Ph	Hx	H	Ph
6-5	m-NO_2Ph	6-HOHx	H	Ph
6-6	m-NO_2Ph	Cim	H	Ph
6-7	m-NO_2Ph	Me	H	p-FPh
6-8	m-NO_2Ph	iPr	H	p-FPh
6-9	2,3-diClPh	Et	H	Ph
6-10	2,3-diClPh	iPr	H	Ph
6-11	2,3-diClPh	Hx	H	Ph
6-12	o-NO_2Ph	Me	H	Ph
6-13	o-NO_2Ph	iPr	H	Ph
6-14	m-NO_2Ph	Me	3-Me	Ph
6-15	m-NO_2Ph	iPr	3-Me	Ph

TABLE 7

Compound No.	n	R^{2b}
7-1	1	4-FPh
7-2	1	4-ClPh
7-3	2	4-FPh
7-4	2	4-ClPh
7-5	3	4-FPh
7-6	3	4-ClPh

Of the compounds listed above, the following are preferred, that is to say Compounds No.

1-9. 3-(1-Benzhydryl-3-azetidinyl) 5-ethyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof;

1-11. 3-(1-Benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof, especially its dihydrochloride;

1-27. 3-(1-Benzhydryl-3-azetidinyl) 5-cyclohexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof, especially its dihydrochloride;

1-59. 3-(1-Benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-4-(2,3-dichlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof;

1-68. 3-[1-(4,4'-Difluorobenzhydryl)-3-azetidinyl] 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof;

1-82. 3-(1-Benzhydryl-3-methyl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof;

2-8. 3-(1-Benzhydryl-3-pyrrolidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)1,4-dihydropyridine-3,5-dicarboxylate and salts thereof, especially its dihydrochloride;

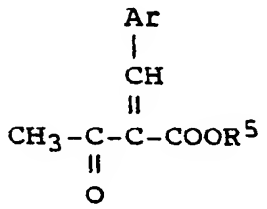
2-9. 3-(1-Benzhydryl-3-pyrrolidinyl) 5-hexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof, especially its dihydrochloride;

3-8. 3-(1-Benzhydryl-3-piperidyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof, especially its dihydrochloride; and

4-3. 3-Isopropyl 5-(1-benzhydryl-3-azetidinyl) 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and salts thereof.

Of these, Compounds No. 1-11, 1-59 and 1-68 are most preferred.

The compounds of formula (I) in accordance with the present invention can be prepared, for example, by the following reaction, specifically, they can be prepared by reacting an α-benzylideneacetoacetic acid ester of formula (II):

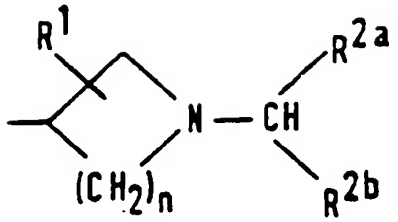


(II)

with an amidinoacetic acid ester of formula (III):

(III)

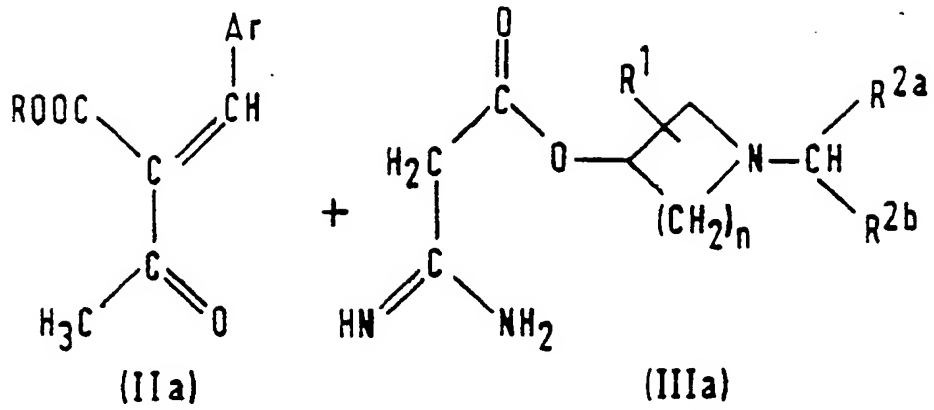
In the above formulae, Ar is as defined above and one of R^5 and R^6 represents a group of formula (IV):



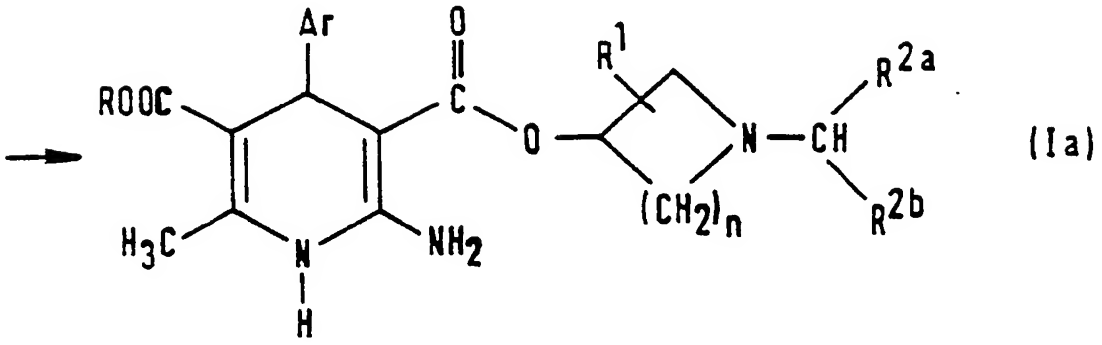
(IV)

(in which n, R^1, R^{2a} and R^{2b} are as defined above) and the other of R^5 and R^6 represents a C_1 -C_{16} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_4 alkyl group having a C_3 -C_6 cycloalkyl substituent, a C_2 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{16} alkyl group having at least one substituent selected from hydroxy, C_1 -C_4 alkoxy and C_1 -C_4 alkylthio groups, i.e. any one of the groups defined above in respect of R.

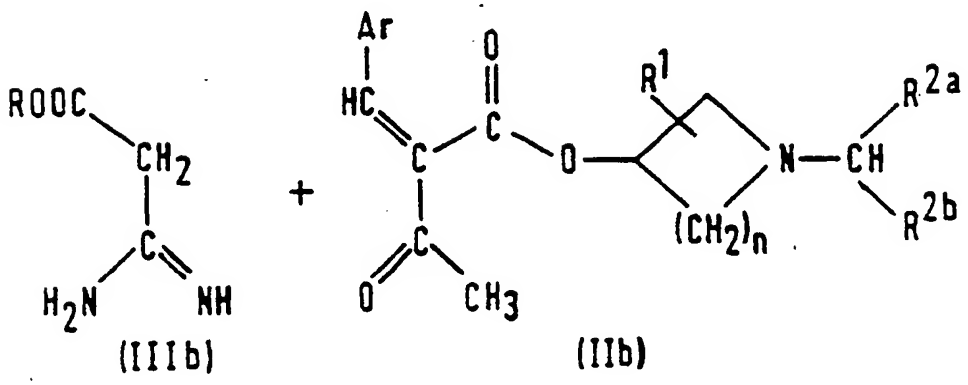
More specifically, the reaction involved in the preparation of the compounds of the invention may be as illustrated below in order to prepare the compounds may be as formulae (Ia) and (Ib), respectively:



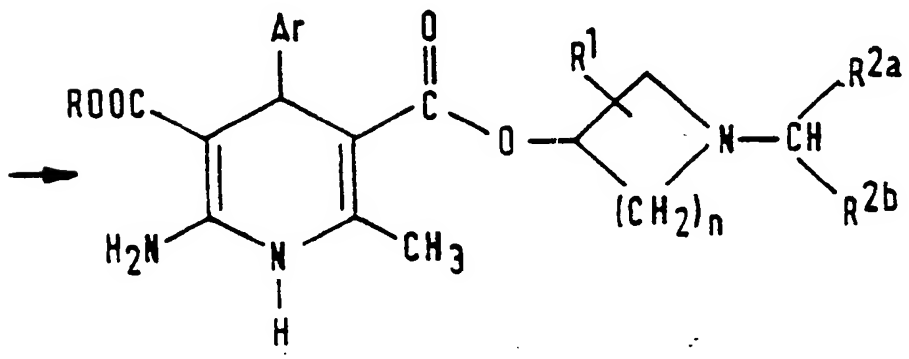
(IIa) (IIIa)



(Ia)



(IIIb) (IIb)



(Ib)

In the above formulae, Ar, n, R, R^1, R^{2a} and R^{2b} are as defined above.

In order to carry out this reaction, the compound of formula (II), (IIa) or (IIb) is mixed with the compound of formula (III), (IIIa) or (IIIb), preferably in equimolar amounts, although a greater than equimolar amount of either of the reagents may be employed, if desired. However, this tends to be wasteful of reagents and so equimolar proportions are preferred. The reaction is preferably carried out in the presence of a solvent, more preferably an organic solvent, for example: an alcohol, such as ethanol, isopropanol or t-butanol; an ether, such as dioxane; a fatty acid amide, such as dimethylformamide; a sulphoxide, such as dimethyl sulphoxide; or a nitrile, such as acetonitrile; or in the presence of water; or a mixture of any two or more thereof. Alternatively, the reaction may be effected in the absence of a solvent.

The reaction will take place over a wide range of temperatures, and the precise temperature chosen is not critical to the present invention. However, we generally find it convenient to carry out the reaction at about room temperature or with heating, preferably at or about the reflux temperature of the reaction mixture, and normally at or about the reflux temperature of the solvent if a solvent is employed. Normally, we prefer to carry out the reaction under atmospheric pressure or under superatmospheric pressure. Most conveniently, the reaction is carried out in the presence of one or more of the above solvents under atmospheric pressure and at around the boiling point of the solvent employed.

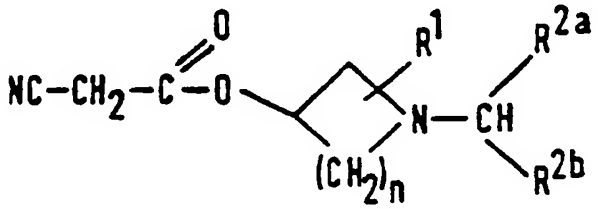
The reaction time will vary depending upon many factors, notably the reaction temperature, and is not critical to the practice of the present invention. However, at the temperatures suggested above, a period of from 30 minutes to five hours will usually suffice.

In this reaction, the compound of formula (III), (IIIa) or (IIIb) is preferably used in the form of an acid addition salt, such as the hydrochloride, hydrobromide or acetate and, in that case the reaction is preferably carried out in the presence of a base, preferably an equimolar amount of a base, and preferably an alkali metal (e.g. sodium or potassium) alkoxide, such as sodium methoxide or sodium ethoxide.

After the completion of the reaction, the desired compound of formula (I), (Ia) or (Ib) may be recovered from the reaction mixture by conventional means, and, if necessary, it may be further purified by such conventional purification techniques as recrystallization or the various chromatography techniques, notably column chromatography.

Of the starting materials employed in the reactions described above, the compound of formula (IIa) may be prepared by the dehydrating condensation of an aldehyde of formula Ar-CHO with an acetoacetic acid ester of formula CH_3COCH_2COOR according to a known method [e.g., G. Jones, "Knoevenagel Condensation", Org. Reactions, Volume 15, 204 (1967)]. The acetoacetic ester employed in this reaction may be prepared from diketene and an alcohol of formula R-OH according to a known method [e.g., A. B. Boese, Jr., Industrial and Engineering Chemistry, 32, 16 (1940)]. In the above formulae, Ar and R are as defined above.

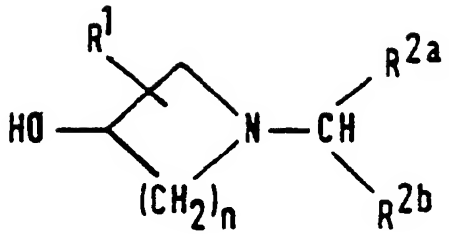
The compound of formula (IIIa) can easily be prepared by reacting a cyanoacetic acid ester of formula (V):



(V)

(in which n, R^1, R^{2a} and R^{2b} are as defined above) with ammonia or with an ammonium salt according to a known method [S. A. Glickman and A. C. Cope, J. Amer. Chem. Soc., 67, 1017 (1945); S. M. McElvain and B. E. Tate, J. Amer. Chem. Soc., 73, 2760 (1951)].

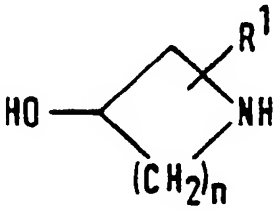
The compound of formula (V) can be prepared by a conventional esterification between cyanoacetic acid and an alcohol of formula (VI):



(VI)

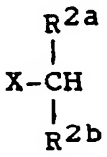
(in which n, R^1, R^{2a} and R^{2b} are as defined above), e.g. a dehydration reaction catalyzed with an acid or in the presence of a carbodiimide, such as 1,3-dicyclohexylcarbodiimide.

The alcohol of formula (VI) can easily be prepared by reacting a cyclic amine of formula (VII):



(VII)

(in which n and R^1 are as defined above) with an optionally substituted benzhydryl halide of formula (VIII):

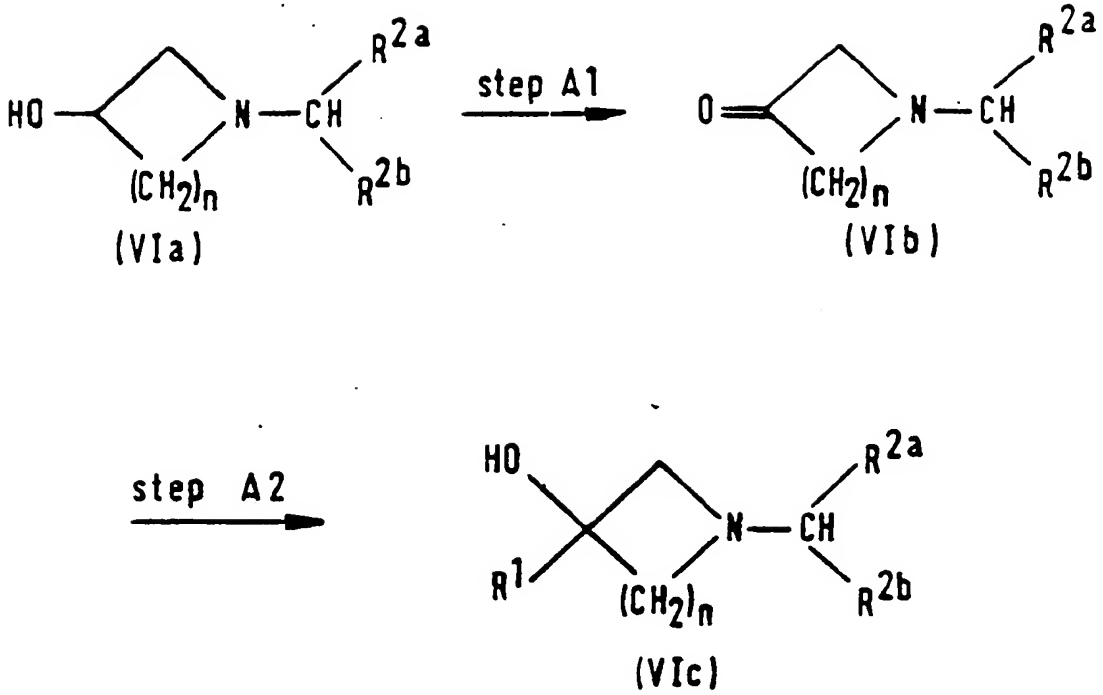


(VIII)

(in which R^{2a} and R^{2b} are as defined above and X represents a halogen atom).

The alcohol of formula (VI) in which n is 1 can be prepared from epichlorohydrin and benzhydrylamine according to a known method [e.g. A. G. Anderson, Jr. and R. Lok., J Org. Chem., 37, 3953(1972)]

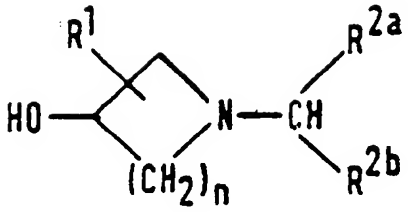
Compounds of formula (VI) in which R^1 represents a C_1 -C_3 alkyl group on the 3-position of the nitrogen-containing heterocyclic ring (i.e. on the same carbon atom as the hydroxy group), that is to say compounds of formula (VIc), may also be prepared as illustrated by the following reaction scheme:



(in which n, R^1, and R^{2a} and R^{2b} are as defined above).

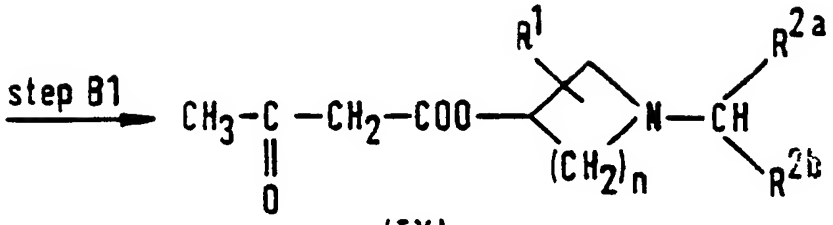
Step A1 of the above reaction scheme, in which the hydroxy group is oxidised to a ketonic oxo group, may be carried out as described by A. Morimoto et al.[Chem. Pharm. Bull., 21, (1), 228 - 231 (1973)] and D. Horton et al. [Carbohydr. Res., 7, 56 (1968)]. Step A2 of the reaction scheme involves the reaction of the compound of formula (VIb), prepared in Step A1, with a Grignard compound of formula R^1MgX' (in which R^1 is as defined above and X' represents a halogen atom, preferably a chlorine, iodine or bromine atom), as described by S. S. Chatterjee et al. [Synthesis, 1973, 153 - 154].

Compounds of formulae (IIb) and (IIIb) may be prepared by methods analogous to those used to prepare the compounds of formulae (IIa) and (IIb), respectively, e.g. as illustrated by the following reaction - schemes:

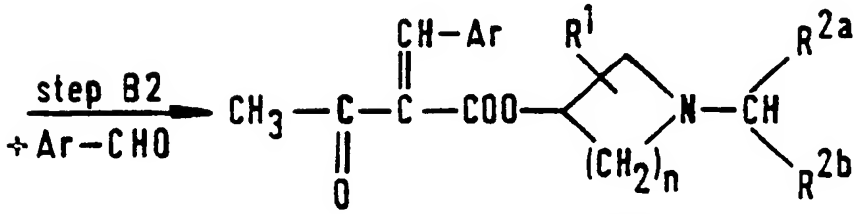


(VIa)

+ diketene

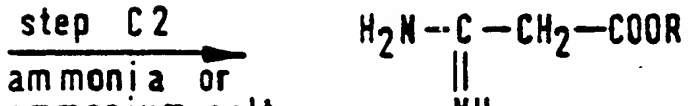


(IX)



(IIb)

R-OH + cyanoacetic acid $\xrightarrow{\text{step C1}}$ $NCCH_2COOR$ (X)



(IIIb)

In the above formulae, Ar, n, R, R^1, R^{2a} and R^{2b} are as defined above.

Steps B1 and B2 of this reaction scheme consist of the reaction of a compound of formula (VIa) with diketene and then the reaction of the resulting acetoacetate compound of formula (IX) with a compound of formula Ar-CHO (Ar being as defined above), in a similar manner to that described for the synthesis of the compound of formula (IIa). Steps C1 and C2 of the reaction scheme consist of the reaction of an alcohol of formula R-OH (R being as defined above) with cyanoacetic acid and then reaction of the resulting cyanoacetate (X) with ammonia or with an ammonium salt in a similar manner to that described for the synthesis of the compound of formula (IIIa).

Compounds of formulae (Ia) and (Ib) synthesized according to the reactions described above can form a number of stereoisomers, for example optical isomers, because of the presence in their molecules of a number of asymmetric carbon atoms, e.g. at the 4-position of the dihydropyridine ring or in the alcohol moiety which forms the ester group. Geometric isomers (cis or trans) may also be formed in some cases as a result of the same alcohol moiety. The individual isolated isomers may, in some cases, be prepared by stereospecific synthesis techniques or they may be isolated by methods known per se from mixtures of isomers. The present invention embraces both the individual isolated isomers and mixtures or isomers.

BIOLOGICAL ACTIVITY

The dihydropyridine derivatives of the present invention exhibit significant calcium antagonism and antihypertensive activity as shown below.

1. Calcium Antagonism

An isolated rat aorta was suspended in a calcium-free and high potassium Krebs-Henseleit solution maintained at a temperature of 37°C. The contractile response of the aorta to calcium chloride in concentrations ranging from 10^{-5} to 10^{-2}M was recorded by means of an isometric transducer. The dose-response curve of the aorta was obtained before and after addition of a test compound at a concentration of 5nM. Addition of the test compound shifted the dose-response curve to the right, the magnitude of the shift depending upon the potency of the Ca^{++}-blocking activity. The test compounds showed a significant rightwards movement and, for example, that of Compound No. 1-11 (see foregoing Table 1), i.e. the compound of Example 1, was comparable with that of nifedipine, and had excellent duration of activity.

2. Antihypertensive activity

The test animals were spontaneously hypertensive rats of the SHR strain, each aged about 15 weeks. The antihypertensive activities of the test compounds were determined in these rats as follows.

Each animal was anaesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally) and polyethylene cannula was inserted into the abdominal aorta by the method of Weeks and Jones [J.R. Weeks and J.A. Jones, Proc. Soc. Exptl. Biol. Med., 104, 646 - 648 (1960)]. The other end of the cannula left the animal's body at, and was fixed to, the neck. About 1 week after this surgery, when the animal had completely recovered from surgical stress, the free end of the aortic cannula was connected to a sphygmomanometer to measure blood pressure and heart rate of the animal directly in the conscious, aparalytic and unrestrained state.

The blood pressure and heart rate were monitored, and, when these had stabilized, which was after about 1 hour, the stable values were recorded as control values. At this time, a test compound suspended in a 0.3 % w/v aqueous carboxymethylcellulose solution was administered orally in the dose shown in the following Table 8. The blood pressure and heart rate were then recorded every 15 minutes during the 24 hours after administration of the test compound.

The experiment was carried out with Compounds No. 1-11, 1-59, 1-68, 2-8 and 3-8 (see foregoing Tables 1, 2 and 3) as well as with nifedipine and nicardipine, and the results are recorded in the following Table 8.

TABLE 8

Cpd. No.	Ex. No.	Dose (mg/kg, po)	12 Hour Area	T_{max} (hours)	$T_{0.5\ max}$ (hours)
1-11	1	1	-184	6.0	10.4
1-11	1	3	-334	5.0	12.7
1-59	7	1	-203	6.0	12.0
1-68	11	1	-218	7.0	11.8
2-8	14	1	-172	6.0	11.2
3-8	16	1	-141	7.0	11.4
nifedipine	-	3	-237	0.3	7.0
nicardipine	-	3	-175	0.5	5.3

In the above Table, the results are reported as follows:

T_{max}: the time in hours after administration of the compound under test before the maximum change in blood pressure was recorded;

$T_{0.5\ max}$: the time in hours after administration of the compound under test which is required for the blood pressure to return to one half of its maximum value;

12 hour area: the integrated value of the area above the graph of blood pressure change against time after administration of the compound under test over a period of 12 hours after administration to show the potency of the blood pressure lowering action.

Although the maximum levels of hypotension produced by all of the compounds of the invention tested were found to be comparable with those produced by nifedipine and nicardipine, there was a considerable difference in the time of onset of activity and in the duration of activity between the compounds of the present invention and the prior art compounds used for comparison. As is obvious from the results reported in Table 8, Compound 1-11 lowered blood pressure much more slowly than did nifedipine or nicardipine, which was an unexpected advantage of Compound 1-11. Also the duration of the antihypertensive activity produced by Compound 1-11 was much longer than that produced by nifedipine and nicardipine. In addition, nifedipine (but not Compound 1-11) increased heart rate, which was most probable caused be a baroreceptor reflex due to the abrupt reduction in blood pressure. Similarly good results were achieved with the other compounds of the invention which we tested.

Accordingly, the compounds of the invention and pharmaceutically acceptable acid addition salts thereof can be used for the treatment of cardiovascular diseases, such as hypertension, angina pectoris miocardial infarction, arrhythmia, arteriosclerosis and cerebrovascular disorders, such as cerebral ischaemia.

The compounds may be administered in any suitable form, depending upon the nature and condition of the patient, the nature of the disorder and the desired route of administration. For example, the compounds may be administered orally in the form of tablets, capsules, granules, powders or syrups. Alternatively, the compounds may be administered non-orally by, for example, subcutaneous injection, intravenous injection or suppository. The compounds may, if desired, be mixed with carriers, excipients or other auxiliary substances commonly employed in the formulation of pharmaceutical preparations, for example diluents, binders, disintegrating agents, lubricants, flavours, solubilizers and suspending agents. The dose will vary, depending upon the symptoms, age and body weight of the patient, as well as the nature and severity of the disease or disorder to be treated; however, a dose of from 3 to 300 mg per day will normally be appropriate for an adult human patient, and this may be administered in a single dose or in divided doses.

The invention is further illustrated with reference to the following Examples. Preparation of certain of the starting materials employed in these Examples is also illustrated in the subsequent Preparations.

EXAMPLE 1

3-(1-Benzhydryl-3-azetidinyl)-5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and its dihydrochloride

Preparation of free base

0.27 g (0.005 mole) of sodium methoxide was added to a solution of 1.39 g (0,005 mole) of isopropyl 2-(3-nitrobenzylidene)acetoacetate and 1.62 g (0.005 mole) of the acetic acid salt of 1-benzhydryl-3-azetidinyl amidinoacetate (prepared as described in Preparation 2) dissolved in 80 ml of isopropanol, and the mixture was heated under reflux for 4 hours. At the end of this time, the mixture was cooled, insoluble materials were filtered off and the filtrate was concentrated by evaporation under reduced pressure. The residue was dissolved in ethyl acetate and washed with water, after which it was dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, and the residue was subjected to column chromatography through silica gel, using a 3 : 1 by volume mixture of toluene and ethyl acetate as eluent, to give 2.17 g (yield 74%) of the title compound (a free base) as pale yellow crystals, melting at 95 - 98°C. Infrared Absorption Spectrum (KBr) $\nu_{max}cm^{-1}$:
3450, 3310 (NH) and 1675 ($-CO_2-$).

Mass Spectrum (CI) m/e : 583 ($M^+ + 1$), 344 (M^+ -benzhydrylazetidinyloxy) and 167 [$^+CH(phenyl)_2$].
Nuclear Magnetic Resonance Spectrum: ($CDCl_3$) δ ppm:
1.08, 1.26 (6H, 2 × doublet, J = 6Hz);
2.35 (3H, singlet);
2.63, 3.06, 3.50, 3.62 (4H, 4 × triplet, J = 8Hz);
4.26 (1H, singlet);
4.87-5.04 (3H, multiplet);
6.04 (1H, broad singlet);
6.11 (2H, broad singlet);
7.1-8.17 (14H, multiplet)

The resulting free base was recrystallized from a mixture of benzene and hexane to afford pale yellow crystals, melting at 120 - 124°C.

The free base was also recrystallized from a mixture of 1,2-dimethoxyethane and hexane to afford pale yellow crystals melting at 162.5 - 164.5°C. The crystals contained an equimolar amount of 1,2-dimethoxyethane (determined by NMR spectrum). These crystals were dried above 100°C under reduced pressure, giving the desired compound as yellow crystals melting at 158 - 160°C.

Both kinds of crystals described above melting at 120 - 124°C and at 158 - 160°C were identified with the free base by NMR spectroscopy.

Elemental analysis:

Calculated for $C_{33}H_{34}N_4O_6$: C, 68.03%; H, 5.88%; N, 9.62%

Found: C, 68.36%; H, 5.94%; N, 9.20%. (free base)
C, 68.49%; H, 5.71%; N, 9.62%. (after recrystallization from a mixture of benzene and hexane)
C, 67.94%; H, 5.91%; N, 9.63 (after recrystallization from a mixture of 1.2-dimethoxyethane and hexane and drying at about 100°C under reduced pressure).

Preparation of dihydrochloride

Hydrogen chloride was bubbled into a solution of 0.87 g of the free base in 20 ml of chloroform for 5 minutes. At the end of this time, the solvent was removed by evaporation under reduced pressure, giving 0.95 g of the title compound dihydrochloride as pale yellow crystals, melting at 118 - 120°C. Infrared Absorption Spectrum: (KBr) ν_{max} cm^{-1}:
3400, 3280 (NH) and 1685 ($-CO_2-$).

Mass Spectrum: m/e : 583 ($M^+ + 1$), 539
[$M^+ - CH(CH_3)_2$], and 167 [$^+CH(phenyl)_2$].

Elemental Analysis: Calculated for $C_{33}H_{36}N_4O_6Cl_2$:
C, 60.46%; H, 5.53%; N, 8.55%.
Found: C, 60.59%; H, 5.81%; N, 8.44%.

EXAMPLES 2 - 18

Following a procedure similar to that described in Example 1, the following compounds were obtained:

Example 2

3-(1-Benzhydryl-3-azetidinyl) 5-methyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, melting at 88 - 92°C.

Example 3

3-(1-Benzhydryl-3-azetidinyl) 5-hexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dihydrochloride, melting at 106 - 108°C.

Example 4

3-(1-Benzhydryl-3-azetidinyl) 5-(2-methoxyethyl) 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, melting at 83 - 85°C.

Example 5

3-(1-Benzhydryl-3-azetidinyl) 5-cinnamyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrate, melting at 114 - 117°C.

Example 6

3-(1-Benzhydryl-3-azetidinyl) 5-cyclohexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dihydrochloride, melting at 113 - 114.5°C.

Example 7

3-(1-Benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-4-(2,3-dichlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate, melting at 100 - 102°C.

Example 8

3-(1-Benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate, melting at 85 - 88°C.

Example 9

3-(1-Benzhydryl-3-azetidinyl) 5-ethyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hemihydrate, melting at 134 - 136°C.

Example 10

3-(1-Benzhydryl-3-azetidinyl) 5-cyclopropylmethyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, melting at 156 - 160°C.

Example 11

3-[1-(4,4'-Difluorobenzhydryl)-3-azetidinyl] 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, melting at 118 - 120°C.

Example 12

3-(1-Benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-trifluoromethylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrate, melting at 96 - 98°C.

Example 13

3-(1-Benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-4-(3-cyanophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate hydrate, melting at 95 - 97°C.

Example 14

3-(1-Benzhydryl-3-pyrrolidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dihydrochloride, melting at 166 - 169°C.

Example 15

3-(1-Benzhydryl-3-pyrrolidinyl) 5-hexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dihydrochloride hydrate, melting at 104 - 108°C.

Example 16

3-(1-Benzhydryl-3-piperidyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dihydrochloride hydrate, melting at 174 - 177°C.

Example 17

3-(1-Benzhydryl-3-piperidyl) 5-hexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dihydrochloride hydrate, melting at 151 - 155°C.

Example 18

3-(1-Benzhydryl-3-methyl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, melting at 116 - 118°C.

Example 19

3-Isopropyl 5-(1-benzhydryl-3-azetidinyl) 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

1.6 g (0.0035 mole) of 1-benzhydryl-3-azetidinyl 2-(3-nitrobenzylidene) acetoacetate (prepared as described in Preparation 15) and 0.63 g (0.0035 mole) of isopropyl amidinoacetate hydrochloride were dissolved in 40 ml of isopropanol. 0.19 g (0.0035 mole) of sodium methoxide was then added to the mixture, and the mixture was heated under reflux for 4 hours. At the end of this time, the mixture was cooled, and the insoluble material was removed by filtration. The solvent was then distilled off under reduced pressure, and the residue was dissolved in ethyl acetate. The resulting solution was washed with water and dried over anhydrous sodium sulphate. The solvent was again distilled off under reduced pressure. The residue was purified by silica gel column chromatography, using a 4 : 1 by volume mixture of toluene and ethyl acetate as eluent, to give 1.15 g (yield 56%) of the title compound as pale yellow crystals, melting at 104 - 107°C. Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:
3440, 3320 (-NH), 1675 (-CO_2-).

Mass Spectrum (CI, m/e): 583 (M^+ + 1), 167 [$^+$CH(phenyl)$_2$].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.04, 1.30 (6H, 2 × doublet, J = 6Hz);
2.32 (3H, singlet);
2.65, 3.00, 3.55 (4H, multiplet);
4.25 (1H, singlet);
4.85-5.05 (3H, multiplet);
6.05 (1H, broad singlet);
6.11 (2H, broad singlet);
7.1 -8.15 (14H, multiplet).

Elemental analysis:
Calculated for $C_{33}H_{34}N_4O_6$:
C, 68.03%, H, 5.88%; N, 9.62%.
Found: C, 68.12%; H, 5.99%; N, 9.40%.

EXAMPLES 20 + 21

The compounds described below were obtained in a similar manner to that described in Example 19.

Example 20

3-Isopropyl 5-(1-benzhydryl-3-pyrrolidinyl) 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, melting at 107 - 110°C

Example 21

3-Isopropyl 5-(1-benzhydryl-3-piperidyl) 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, melting at 112 - 116°C

PREPARATION 1

1-Benzhydryl-3-azetidinyl cyanoacetate

4.25 g (0.05 mole) of cyanoacetic acid and 11.95 g (0.05 mole) of 1-benzhydryl-3-hydroxyazetidine were dissolved in 400 ml of tetrahydrofuran. 12.38 g (0.06 mole) of 1,3-dicyclohexylcarbodiimide were then added to the solution, whilst stirring, after which the mixture was stirred at 55°C for a further 11 hours. At the end of this time, the mixture was cooled, precipitated crystals were removed and the solvent was removed by distillation under reduced pressure. The residue was dissolved in ethyl acetate and the resulting solution was washed with water and then dried over anhydrous sodium sulphate.

The solution was then concentrated by evaporation under reduced pressure, and the residue was subjected to column chromatography through silica gel, using a 19 : 1 by volume mixture of toluene and ethyl acetate as eluent, to give 14.25 g (93%) of the title compound as a pale yellow oil. Infrared Absorption Spectrum (capillary) ν_{max} cm^{-1}:
2250 (CN) and 1745 ($-CO_2-$).

Mass Spectrum m/e: 306 (M^+) and 167
[$^+CH(phenyl)_2$].

Nuclear Magnetic Resonance Spectrum: ($CDCl_3$) δ ppm:

3.1 (2H, multiplet);
3.46 (2H, singlet);
3.6 (2H, multiplet);
4.37 (1H, singlet);
5.16 (1H, quartet, J = 6 Hz);
7.1-7.5 (10H, multiplet).

PREPARATION 2

Acetic acid salt of 1-benzhydryl-3-azetidinyl amidinoacetate

A solution of 7.0 g (0.0229 mole) of 1-benzhydryl-3-azetidinyl cyanoacetate (prepared as described in Preparation 1) and 1.26 g (0.0275 mole) of ethanol dissolved in 300 ml of chloroform was cooled with a mixture of salt and ice. Hydrogen chloride was then bubbled into the solution for 30 minutes, whilst cooling, and the mixture was allowed to stand overnight, also whilst cooling. At the end of this time, the temperature of the mixture was allowed to rise to room temperature, and then the mixture was freed from the solvent by evaporation under reduced pressure. The residue was dissolved in 300 ml of chloroform and ammonia was bubbled into the solution for 1 hour, whilst ice-cooling. The precipitated salt was removed by filtration, and the solvent was distilled off under reduced pressure. The residue was dissolved in 50 ml of acetonitrile, and 1.76 g (0.0229 mole) of ammonium acetate was then added to the solution. The mixture was stirred at 55°C for 1 hour. At the end of this time, unreacted ammonium acetate was removed from the still hot reaction mixture by filtration, and the solvent was distilled off under reduced pressure. The residue was crystallized by adding diethyl ether, and the resulting crystals were collected by filtration and then dried under reduced pressure to afford 7.6 g (yield 87% based on the cyanoacetate) of the title compound as colourless crystals, melting at 100 - 103°C. Mass Spectrum m/e: 324 (M^+ + 1) and 167
[$^+CH(phenyl)_2$].

PREPARATION 3

1-(4,4'-Difluorobenzhydryl)-3-hydroxyazetidine

9.25 g (0.1 mole) of epichlorohydrin and 21.9 g (0.1 mole) of 4,4'-difluorobenzhydrylamine were dissolved in 100 ml of methanol. The mixture was stirred at room temperature whilst shading it from the light for 3 days. At the end of this time, the mixture was heated under reflux whilst stirring for 3 days. The methanol was then distilled off under reduced pressure, and the residue was dissolved in ethyl acetate. The resulting solution was washed, first with 100 ml of a 10% w/v aqueous solution of sodium hydroxide and then twice, each time with 100 ml of water. The organic layer was dried over anhydrous sodium sulphate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography, using a 3 : 2 by volume mixture of toluene and ethyl acetate as eluent, to give 6 g (yield 22 %) of the title compound as a pale yellow oil. Infrared Absorption Spectrum (capillary) ν_{max} cm^{-1}: 3360 (-OH).

Mass Spectrum (m/e): 275 (M^+), 203 [$^+$CH(p-fluorophenyl)$_2$].

Nuclear Magnetic Resonance Spectrum CDCℓ_3) δ ppm:

2.35 (1H, singlet);
2.86 (2H, multiplet);
3.46 (2H, multiplet);
4.30 (1H, singlet);
4.40 (1H, quintet, J = 5 Hz);
6.88-7.35 (8H, multiplet).

PREPARATION 4

1-Benzhydryl-3-hydroxy-3-methylazetidine

(a) 7.17 g (0.03 mole) of 1-benzhydryl-3-hydroxy-azetidine were dissolved in a mixture of 35 ml of dimethyl sulphoxide and 20 ml of methylene chloride. 1 ml of pyridine 0.5 ml of phosphoric acid and then 12.5 g (0.06 mole) of 1,3-dicyclohexylcarbodiimide were added, in turn, to the resulting solution. The reaction mixture was then stirred for 2 hours, after which water was added to it. The reaction mixture was then extracted twice, each time with 200 ml of chloroform. The combined extracts were dried over anhydrous sodium sulphate, and the solvent was then distilled off under reduced pressure. The concentrate was subjected to silica gel column chromatography, and 4.84 g (67%) of 1-benzhydryl-3-oxoazetidine were obtained from the fractions eluted with a 9 : 1 by volume mixture of toluene and ethyl acetate. Mass Spectrum (CI, m/e):238 (M^+ + 1), 167 [$^+$CH(phenyl)$_2$].

(b) 7.26 g (0.03 mole) of 1-benzhydryl-3-oxoazetidine [obtained as described in step (a) above] were dissolved in 50 ml of diethyl ether. 60 ml of a 1M tetrahydrofuran solution of methylmagnesium bromide were then added to this solution, whilst ice-cooling. The reaction mixture was then stirred for 1 hour, after which 200 ml of water were added to it. The mixture was then extracted with 100 ml of diethyl ether. The organic extract was dried over anhydrous sodium sulphate, and the solvent was removed by distillation under reduced pressure. The concentrate was subjected to silica gel column chromatography, and 5.92 g (76 %) of the title compound were obtained from the fractions eluted with a 3 : 1 by volume mixture of toluene and ethyl acetate. Mass Spectrum (CI, m/e): 254 (M^+ + 1), 167 [$^+$CH(phenyl)$_2$].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.5 (3H, singlet);
2.15 (1H, broad);
2.97 (2H, doublet, J = 8 Hz);
3.2 (2H, doublet, J = 8 Hz);
4.35 (1H, singlet);
7.15-7.45 (10H, multiplet).

PREPARATION 5

1-Benzhydryl-3-hydroxypiperidine

5.05 g (0.05 mole) of 3-hydroxypiperidine and 13.82 g (0.1 mole) of potassium carbonate were suspended in 100 ml of dimethylformamide. 12.36 g (0.05 mole) of benzhydryl bromide were then added to the mixture, whilst stirring, and the mixture was stirred for 10 hours at room temperature. At the end of this time, the mixture was poured into 700 ml of water and extracted with ethyl acetate. The extracts were washed with water and dried over anhydrous sodium sulphate. The solvent was then distilled off under reduced pressure. The residue was subjected to silica gel column chromatography, and 10.53 g (yield 78%) of the title compound were obtained as a colourless material from the fractions eluted with a 9 : 1 by volume mixture of toluene and ethyl acetate.

Infrared Absorption Spectrum (capillary) ν_{max} cm^{-1}: 3340 (-OH).

Mass Spectrum (m/e): 267 (M^+), 167 [$^+CH(phenyl)_2$].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.4-2.5 (9H, multiplet);
3.8. (1H, singlet);
4.3 (1H, singlet);
7.13-7.4 (10H, multiplet).

PREPARATION 6

1-Benzhydryl-3-hydroxypyrrolidine

Following a procedure similar to that described in Preparation 5, except that 4.35 g (0.05 mole) of 3-hydroxypyrrolidine were used instead of the 3-hydroxypiperidine, 10.25 g (yield 81%) of the title compound were obtained.

Infrared Absorption Spectrum (capillary) ν_{max} cm^{-1}: 3360 (-OH).
Mass Spectrum (m/e): 253 (M^+), 167 [$^+CH(phenyl)_2$].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.64-2.82 (7H, multiplet);
4.20 (1H, singlet);
4.29 (1H, multiplet);
7.10-7.47 (10H, multiplet).

PREPARATION 7 - 10

The compounds described below were obtained in a similar manner to that described in Preparation 1.

Preparation 7 1-(4,4'-Difluorobenzhydryl)-3-azetidinyl cyanoacetate

Mass Spectrum (EI, m/e): 342 (M^+), 203
[$^+$CH(p-fluorophenyl)$_2$].

Preparation 8 1-Benzhydryl-3-methyl-3-azetidinyl cyanoacetate

Mass Spectrum (CI, m/e): 321 ($M^+ + 1$), 167
[$^+$CH(phenyl)$_2$].

Preparation 9 1-Benzhydryl-3-pyrrolidinyl cyanoacetate

Mass Spectrum (EI, m/e): 320 (M^+), 167
[$^+$CH(phenyl)$_2$].

Preparation 10 1-Benzhydryl-3-piperidyl cyanoacetate
Mass Spectrum (EI, m/e): 334 (M^+), 167
($^+$CH(phenyl)$_2$)

PREPARATION 11 - 14

The compounds described below are obtained in a similar manner to that described in Preparation 2.

Preparation 11 1-(4,4'-Difluorobenzhydryl)-3-azetidinyl amidinoacetate

Mass Spectrum (CI, m/e): 360 ($M^+ + 1$), 203
[$^+$CH(p-fluorophenyl)$_2$].

Preparation 12 1-Benzhydryl-3-methyl-azetidinyl amidinoacetate

Mass Spectrum (CI, m/e): 338 ($M^+ + 1$), 167
[$^+$CH(phenyl)$_2$].

Preparation 13 1-Benzhydryl-3-pyrrolidinyl amidinoacetate

Mass Spectrum (CI, m/e): 338 (M^+ + 1), 167
[$^+$CH(phenyl)$_2$].

Preparation 14 1-Benzhydryl-3-piperidyl amidinoacetate

Mass Spectrum (CI, m/e): (M^+ + 2), 167
[$^+$CH(phenyl)$_2$].

PREPARATION 15

1-Benzhydryl-3-azetidinyl 2-(3-nitrobenzylidene)-acetoacetate

(a) 11.95 g (0.05 mole) of 1-benzhydryl-3-hydroxy-azetidine and 0.5 ml of triethylamine were dissolved in 50 ml of chloroform. 6.3 g (0.075 mole) of diketene were then added dropwise to the solution, after which the reaction mixture was stirred for 10 hours at room temperature. Water was then added to it, after which the reaction mixture was stirred for a further 30 minutes. At the end of this time, the chloroform layer was separated and dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure. The concentrate was subjected to silica gel column chromatography, and 15.07 g (93%) of 1-benzhydryl-3-azetidinyl acetoacetate were obtained, as a pale yellow oil, from the fractions eluted with a 9 : 1 by volume mixture of toluene and ethyl acetate. Infrared Absorption Spectrum (capillary) ν_{max} cm^{-1}: 1750 (-CO_2-), 1725 (>C=O).

(b) 6.46 g (0.02 mole) of 1-benzhydryl-3-azetidinyl acetoacetate [obtained as described in step (a) above], 3.02 g (0.02 mole) of m-nitrobenzaldehyde and 0.29 g (0.002 mole) of piperidinium acetate were dissolved in 10 ml of a 10 : 1 by volume mixture of toluene and methanol. The reaction mixture was then allowed to stand for 24 hours at room temperature. At the end of this time, ethyl acetate was added to the mixture. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure. The concentrate was subjected to silica gel column chromatography, and 3.20 g (yield 35%) of the title compound were obtained, as a pale yellow oil, from the fractions eluted with a 19 : 1 by volume mixture of toluene and ethyl acetate. Mass Spectrum (CI, m/e): 457 (M^+ + 1), 167
[$^+$CH(phenyl)$_2$].

Infrared Absorption Spectrum (capillary) ν_{max} cm^{-1}: 1640 (-CO_2-).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

2.45 (3H, singlet);
3.05 (2H, multiplet);
3.65 (2H, multiplet);
4.35 (1H, singlet);
5.25 (1H, quintet, J = 6 HZ);
7.1-8.4 (15H, multiplet).

Preparation 16 + 17

The compounds described below were obtained in a similar manner to that described in Preparation 15.

Preparation 161-Benzhydryl-3-pyrrolidinyl 2-(3-nitrobenzylidene)acetoacetate

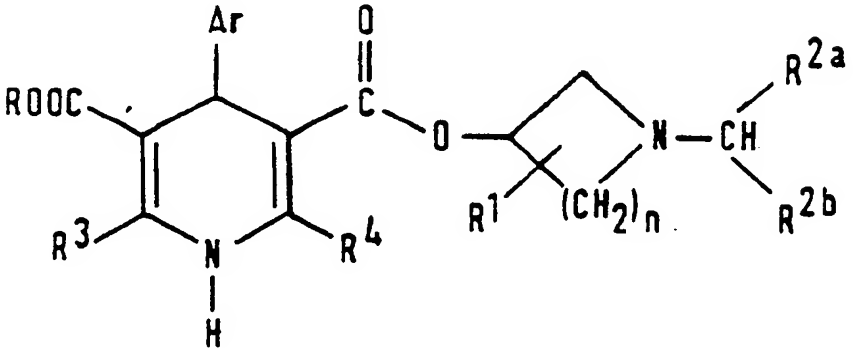
Mass Spectrum (CI, m/e): 471 (M^+ + 1), 167
[$^+$CH(phenyl)$_2$].

Preparation 171-Benzhydryl-3-piperidyl 2-(3-nitrobenzylidene)acetoacetate

Mass Spectrum (CI, m/e): 485 (M^+ + 1), 167
[$^+$CH(phenyl)$_2$].

Claims

1. Compounds of formula (I):



(I)

in which:

Ar represents a phenyl group having at least one substituent selected from nitro, C_1 -C_4 haloalkyl, C_1 -C_4 haloalkoxy and cyano groups and halogen atoms;

R represents a C_1 -C_{16} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_4 alkyl group having a C_3 -C_6 cycloalkyl substituent, a C_2 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{16} alkyl group having at least one substituent selected from hydroxy, C_1 -C_4 alkoxy and C_1 -C_4 alkylthio groups;

R^1 represents a hydrogen atom or a C_1 -C_3 alkyl group;

R^{2a} and R^{2b} are the same or different and each represents an unsubstituted phenyl group or a substituted phenyl group having at least one substituent selected from C_1 -C_4 alkyl, C_1 -C_4 alkoxy and C_1 -C_4 haloalkyl groups and halogen atoms;

one of R^3 and R^4 represents a methyl group and the other represents an amino group; and

n is an integer from 1 to 3;

and pharmaceutically acceptable acid addition salts thereof.

2. Compounds according to Claim 1, in which

Ar represents a phenyl group having a single substituent selected from nitro, C_1 -C_2 haloalkyl, C_1 -C_2 haloalkoxy and cyano groups or having one or two halogen substituents;

R represents a C_1 -C_{10} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_2 alkyl group having a C_3 -C_6 cycloalkyl

substituent, a C_3 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{10} alkyl group having at least one substituent selected from hydroxy, C_1 -C_3 alkoxy and C_1 - C_3 alkoxy and C_1 -C_3 alkylthio groups;

R^1 represents a hydrogen atom or a C_1 -C_3 alkyl group;

R^{2a} and R^{2b} are the same or different and each represents an unsubstituted phenyl group or a substituted phenyl group having at least one substituent selected from C_1 -C_3 alkyl, C_1 -C_3 alkoxy and trifluoromethyl groups and halogen atoms;

one of R^3 and R^4 represents a methyl group and the other represents an amino group; and

n is an integer from 1 to 3.

3. Compounds according to Claim 1, in which:

Ar represents a phenyl group having a single substituent selected from nitro, trifluoromethyl, difluoromethoxy and cyano groups or having one to two chloro substituents;

R represents a C_1 -C_6 alkyl group, an alkoxyalkyl group containing from three to five carbon atoms, an alkylthioalkyl group containing three or four carbon atoms, a cycloalkyl group containing five or six carbon atoms, a cycloalkylalkyl group containing a total of from four to seven carbon atoms, an alkenyl group containing three or four carbon atoms or a cinnamyl group;

R^1 represents a hydrogen atom or a methyl group; and

R^{2a} and R^{2b} are the same and each represents a phenyl group or a phenyl group having a single substituent selected from chlorine atoms, fluorine atoms, trifluoromethyl groups, methyl groups and methoxy groups.

4. Compounds according to Claim 1, in which:

Ar represents a phenyl group having a single substitutent selected from nitro, trifluoromethyl, difluoromethoxy and cyano groups or having one or two chloro substituents;

R represents a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, 2-methoxyethyl, 2-ethoxyethyl, 2-propoxyethyl, 2-methylthioethyl, 3-methylthiopropyl, 2-ethylthioethyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, allyl, 2-butenyl or cinnamyl group;

R^1 represents a hydrogen atom or a methyl group; and

R^{2a} and R^{2b} are the same and each represents a phenyl group or a phenyl group having a single substituent selected from chlorine atoms, fluorine atoms, trifluoromethyl groups, methyl groups and methoxy groups;

5. Compounds according to Claim 1, in which:

Ar represents a 2-nitrophenyl group, a 3-nitrophenyl group, a 2-trifluoromethylphenyl group, a 3-trifluoromethylphenyl group, a 2-chlorophenyl group or a 2,3-dichlorophenyl group;

R represents a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, 2-methoxyethyl, 2-ethoxyethyl, 2-propoxyethyl, 2-methylthioethyl, 3-methylthiopropyl, 2-ethylthioethyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, allyl, 2-butenyl or cinnamyl group;

R^1 represents a hydrogen atom or a methyl group; and

R^{2a} and R^{2b} are the same and each represents a phenyl group or a p-fluorophenyl group.

6. Compounds according to Claim 1 or Claim 2, in which $R^{2a}$and R^{2b} are the same.

7. Compounds according to any one of the preceding Claims, in which R^3 represents a methyl group and R^4 represents an amino group.

8. 3-(1-Benzhydryl-3-azetidinyl) 5-ethyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

9. 3-(1-Benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

10. 3-(1-Benzhydryl-3-azetidinyl) 5-cyclohexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

11. 3-(1-Benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-4-(2,3-dichlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

12. 3-[1-(4,4'-Difluorobenzhydryl)-3-azetidinyl] 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

13. 3-(1-Benzhydryl-3-methyl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

14. 3-(1-Benzhydryl-3-pyrrolidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

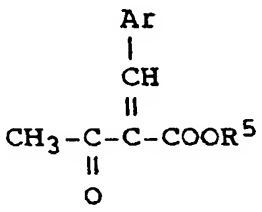
15. 3-(1-Benzhydryl-3-pyrrolidinyl) 5-hexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

16. 3-(1-Benzhydryl-3-piperidyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

17. 3-Isopropyl 5-(1-benzhydryl-3-azetidinyl) 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and pharmaceutically acceptable salts thereof.

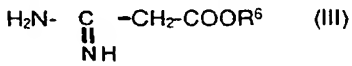
18. A pharmaceutical composition comprising an active compound in admixture with a pharmaceutically acceptable carrier or diluent, in which said active compound is at least one compound according to any one of the preceding Claims.

19. A process for preparing a compound according to any one of Claims 1 to 17, which process comprises reacting an α-benzylideneacetoacetic acid ester of formula (II):



(II)

with an amidinoacetic acid ester of formula (III):

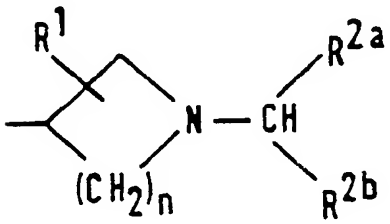


(III)

[in the above formulae:

Ar is as defined in Claim 1; and

one of R^5 and R^6 represents a group of formula (IV):



(IV)

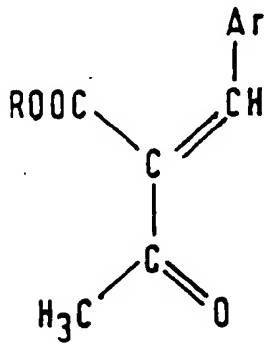
in which n, R^1, R^{2a} and R^{2b} are as defined in Claim 1) and the other of R^5 and R^6 represents a C_1 -C_{16} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_4 alkyl group having a C_3 -C_6 cycloalkyl substituent, a C_2 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{16} alkyl group having at least one substituent selected from hydroxy, C_1 -C_4 alkoxy and C_1 -C_4 alkylthio groups)],

and optionally salifying and/or desalifying the resulting product to give said compound of formula (I) or said

pharmaceutically acceptable acid addition salt thereof.

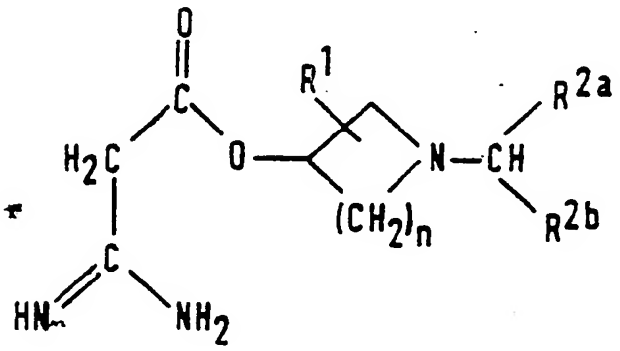
20. A process according to Claim 19, in which, to produce a compound of formula (I) in which R^3 represents a methyl group and R^4 represents an amino group, there is employed a compound of formula (III) in which R^6 represents said group of formula (IV).

21. A process according to Claim 19, in which a compound of formula (IIa):



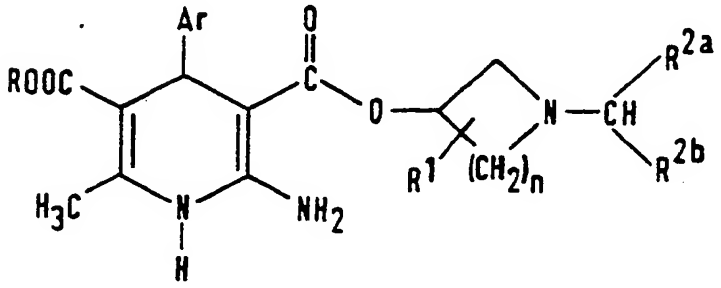
(IIa)

(in which Ar and R are as defined in Claim 1) is reacted with a compound of formula (IIIa):



(IIIa)

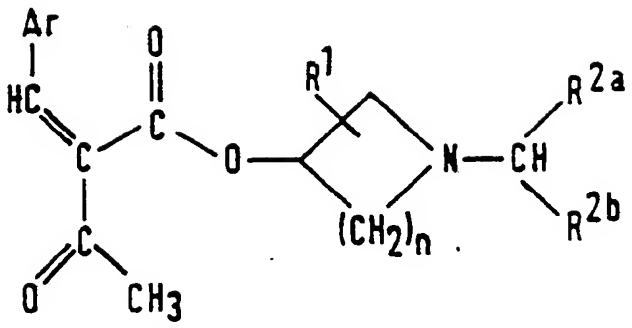
(in which R^1, R^{2a}, R^{2b} and n are as defined in Claim 1), to produce a compound of formula (Ia):



(Ia)

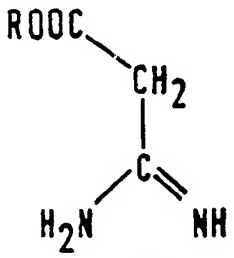
(in which Ar, R, R^1, R^{2a}, R^{2b} and n are as defined in Claim 1).

22. A process according to Claim 19, in which a compound of formula (IIb):



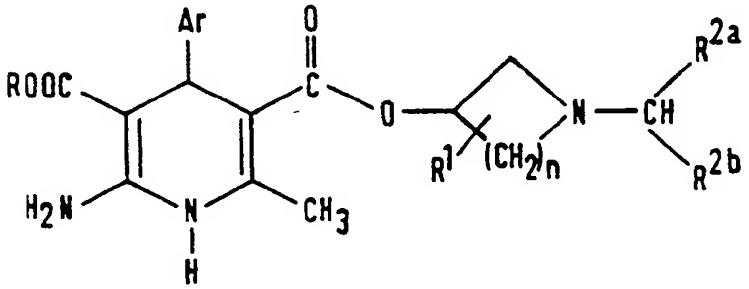
(IIb)

(in which Ar, R^1, R^{2a}, R^{2b} and n are as defined in Claim 1) is reacted with a compound of formula (IIIb):



(IIIb)

(in which R is as defined in Claim 1), to produce a compound of formula (Ib):



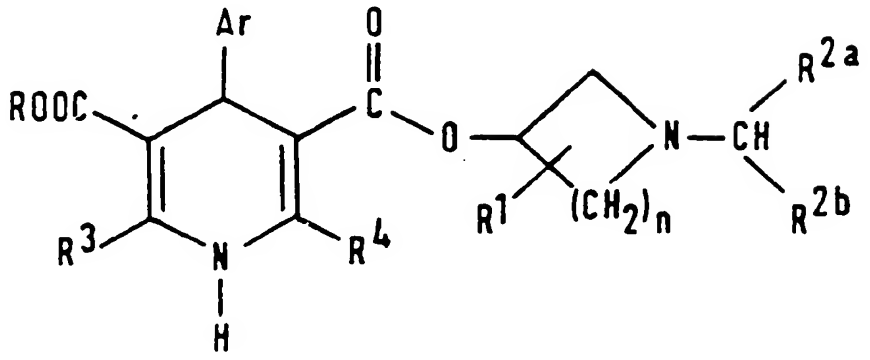
(Ib)

(in which Ar, R, R^1, R^{2a}, R^{2b} and n are as defined in Claim 1).

23. The use for the manufacture of a medicament, especially for the treatment of cardiovascular disorders, of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 17.

Claims for the following Contracting States: AT ES, AT, GR

1. A process for preparing compounds of formula (I):



(I)

[in which:

Ar represents a phenyl group having at least one substituent selected from nitro, C_1 -C_4 haloalkyl, C_1 -C_4 haloalkoxy and cyano groups and halogen atoms;

R represents a C_1 -C_{18} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_4 alkyl group having a C_3 -C_6 cycloalkyl substituent, a C_2 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{16} alkyl group having at least one substituent selected from hydroxy, C_1 -C_4 alkoxy and C_1 -C_4 alkylthio groups;

R^1 represents a hydrogen atom or a C_1 -C_3 alkyl group;

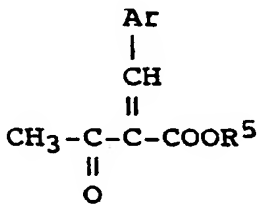
R^{2a} and R^{2b} are the same or different and each represents an unsubstituted phenyl group or a substituted phenyl group having at least one substituent selected from C_1 -C_4 alkyl, C_1 -C_4 alkoxy and haloalkyl groups and halogen atoms;

one of R^3 and R^4 represents a methyl group and the other represents an amino group; and

n is an integer from 1 to 3];

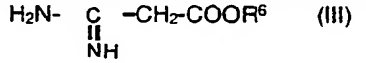
and pharmaceutically acceptable acid addition salts thereof, which process comprises:

reacting an α-benzylideneacetoacetic acid ester of formula (II):



(II)

with an amidinoacetic acid ester of formula (III):

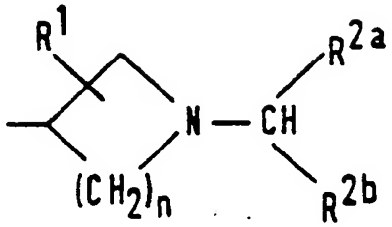


(III)

[in the above formulae:

Ar is as defined above; and

one of R^5 and R^6 represents a group of formula (IV):



(IV)

(in which n R^1, R^{2a} and R^{2b} are as defined above) and the other of R^5 and R^6 represents a C_1 -C_{16} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_4 alkyl group having a C_3 - C_6 cycloalkyl substituent, a C_2 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{16} alkyl group having at least one substituent selected from hydroxy, C_1 -C_4 alkoxy and C_1 -C_4 alkylthio groups)],

and optionally salifying and/or desalifying the resulting product to give said compound of formula (I) or said pharmaceutically acceptable acid addition salt thereof.

2. A process according to Claim 1, wherein:

Ar in said compound of formula (II) represents a phenyl group having a single substituent selected from nitro, C_1 -C_2 haloalkyl, C_1 -C_2 haloalkoxy and cyano groups or having one or two substituents selected from the group consisting of halogen atoms;

one of R^5 and R^6 represents a C_1 -C_{10} alkyl group, a C_3 -C_6 cycloalkyl group, a C_1 -C_2 alkyl group having a C_3 -C_6 cycloalkyl substitutent, a C_3 -C_4 alkenyl group, a cinnamyl group or a C_1 -C_{10} alkyl group having at least one substituent selected from hydroxy, C_1 -C_3 alkoxy and C_1 -C_3 alkylthio groups and the other of R^5 and R^6 represents said group of formula (IV);

R^1 in said group of formula (IV) represents a hydrogen atom or a C_1 -C_3 alkyl group;

R^{2a} and R^{2b} in said group of formula (IV) are the same or different and each represents an unsubstituted phenyl group or a substituted phenyl group having at least one substituent selected from C_1 -C_3 alkyl, C_1 -C_3 alkoxy and trifluormethyl groups and halogen atoms; and

n in said group of formula (IV) is an integer from 1 to 3.

3. A process according to Claim 1 or Claim 2, wherein R^{2a} and R^{2b} in said group of formula (IV) are the same.

4. A process according to Claim 1, wherein:

Ar in said compound of formula (II) represents a phenyl group having a single substituent selected from nitro, trifluoromethyl, difluoromethoxy and cyano groups or having one of two chloro substituents;

one of R^5 and R^6 represents a C_1 -C_6 alkyl group, an alkoxyalkyl group containing from three to five carbon atoms, an alkylthioalkyl group containing three or four carbon atoms, a cycloalkyl group containing five or six carbon atoms, a cycloalkylalkyl group containing a total of from four to seven carbon atoms, an alkenyl group containing three of four carbon atoms or a cinnamyl group and the other of R^5 and R^6 represents said group of formula (IV);

R^1 in said group of formula (IV) represents a hydrogen atom or a methyl group; and

R^{2a} and R^{2b} in said group of formula (IV) are the same and each represents a phenyl group or a phenyl group having a single substituent selected from chlorine atoms, fluorine atoms, trifluoromethyl groups, methyl groups and methoxy groups.

5. A process according to Claim 1, wherein:

Ar in said compound of formula (II) represents a phenyl group having a single substituent selected from nitro, trifluoromethyl, difluoromethoxy and cyano groups or having one or two chloro substituents;

one of R^5 and R^6 represents a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, 2-meth[illegible]l, 2-ethoxyethyl, 2-propoxyethyl, 2-methylthioethyl, 3-methylthiopropyl, 2-methylthioethyl, cyclo[illegible]yl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, allyl, 2-butenyl or cinnamyl group and the other of R^5 and R^6 represents said group of formula (IV);

R^1 in said group of formula (IV) represents a hydrogen atom or a methyl group; and

R^{2a} and R^{2b} in said group of formula (IV) are the same and each represents a phenyl group or a phenyl group having a single substituent selected from chlorine atoms, fluorine atoms, trifluoromethyl groups, methyl groups and methoxy groups;

6. A process according to Claim 1, wherein:

Ar in said compound of formula (II) represents a 2-nitrophenyl group, a 3-nitrophenyl group, a 2-trifluoromethylphenyl group, a 3-trifluoromethylphenyl group, a 2-chlorophenyl group or a 2,3-dichlorophenyl group;

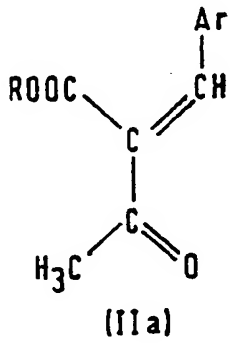
one of R^5 and R^6 represents a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, 2-methoxyethyl, 2-ethoxyethyl, 2-propoxyethyl, 2-methylthioethyl, 3-methylthiopropyl, 2-ethylthioethyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, allyl, 2-butenyl or cinnamyl group and the other of R^5 and R^6 represents said group of formula (IV);

R^1 in said group of formula (IV) represents a hydrogen atom or a methyl group; and

R^{2a} and R^{2b} in said group of formula (IV) are the same and each represents a phenyl group or a p-fluorophenyl group.

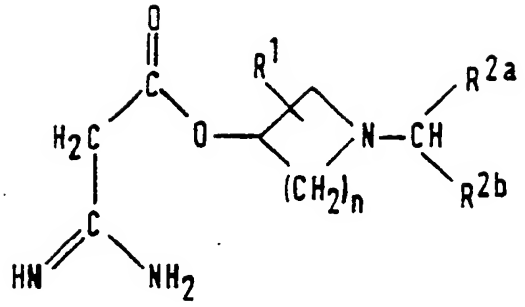
7. A process according to any one of the preceding Claims, wherein, to produce a compound of formula (I) in which R^3 represents a methyl group and R^4 represents an amino group, there is employed a compound of formula (III) in which R^6 represents said group of formula (IV).

8. A process according to any one of Claims 1 to 6, in which a compound of formula (IIa):



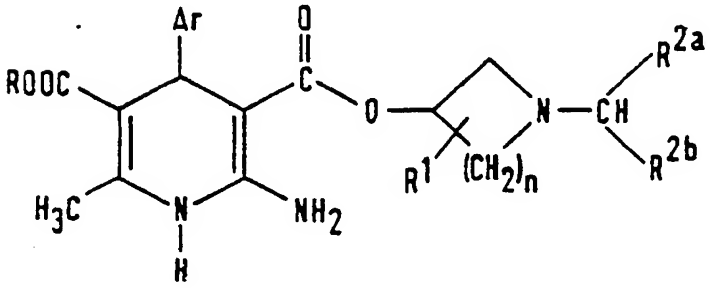
(IIa)

(in which Ar and R are as defined in Claim 1) is reacted with a compound of formula (IIIa):



(IIIa)

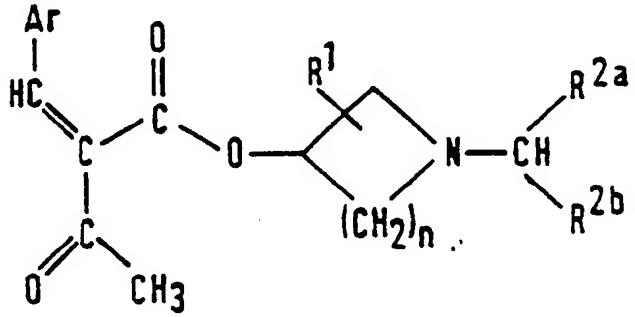
(in which R^1, R^{2a}, R^{2b} and n are as defined in Claim 1), to produce a compound of formula (Ia):



(Ia)

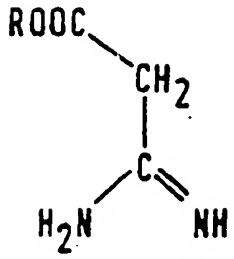
(in which Ar, R, R^1, R^{2a}, R^{2b} and n are as defined in Claim 1).

9. A process according to any one of Claims 1 to 6, in which a compound of formula (IIb):



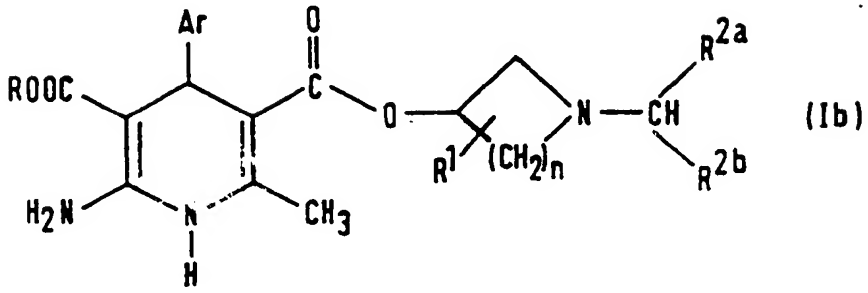
(IIb)

(in which Ar, R^1, R^{2a}, R^{2b} and n are as defined in Claim 1) is reacted with a compound of formula (IIIb):



(IIIb)

(in which R is as defined in Claim 1), to produce a compound of formula (Ib):



(Ib)

(in which Ar, R, R^1, R^{2a}, R^{2b} and n are as defined in Claim 1).

10. A process according to Claim 1, in which the reagents and reaction conditions are so selected as to prepare:

3-(1-benzhydryl-3-azetidinyl) 5-ethyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-azetidinyl) 5-cyclohexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-4-(2,3-dichlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate;

3-[1-(4,4'-difluorobenzhydryl)-3-azetidinyl] 5-isopropyl 2-amino-6-methyl-4-(3-nitrophe[illegible],4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-methyl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-pyrrolidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-pyrrolidinyl) 5-hexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

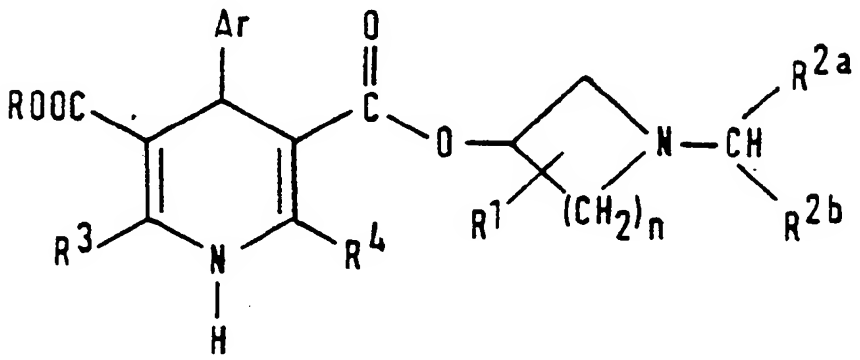
3-(1-benzhydryl-3-piperidyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

or

3-isopropyl 5-(1-benzhydryl-3-azetidinyl) 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

or a pharmaceutically acceptable acid addition salt thereof.

11. The use for the manufacture of a medicament, especially for the treatment of cardiovascular disorders, of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 9.

12. The use for the manufacture of a medicament, especially for the treatment of cardiovascular disorders, of;

3-(1-benzhydryl-3-azetidinyl) 5-ethyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-azetidinyl) 5-cyclohexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-azetidinyl) 5-isopropyl 2-amino-4-(2,3-dichlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate;

3-[1-(4,4'-difluorobenzhydryl)-3-azetidinyl] 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-methyl-3-azetdinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-pyrrolidinyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-pyrrolidinyl) 5-hexyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

3-(1-benzhydryl-3-piperidyl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;

or

3-isopropyl 5-(1-benzhydryl-3-azetidinyl) 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicar-

boxylate;

or a pharmaceutically acceptable acid addition salt thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 30 8976

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.3)
A,D	EP-A-0 125 803 (FISONS PLC) * claims 1, 8-10, page 13, lines 11-16, example 68 * ---	1,18,19 ,23	C 07 D 211/90 C 07 D 401/12 A 61 K 31/44 // C 07 D 205/04 C 07 D 211/46 C 07 D 207/12
L	CHEMICAL ABSTRACTS, vol. 106, no. 5, 2nd February 1987, page 531, column 1, abstract no. 32851b, Columbus, Ohio, US; & JP - A - 61 158 962 (TEIJIN LTD.) 18-07-1986 (Cat. D) ---	1,18,23	
A	GB-A-2 014 134 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) * page 1, lines 5-25, page 2, lines 4-7; examples * ---	1,18,23	
A	EP-A-0 063 365 (KYOWA HAKKO KOGYO CO. LTD.) * page 1, lines 1-13; example 4 * ---	1,18,23	
A	EP-A-0 106 276 (KYOWA HAKKO KOGYO CO. LTD.) * page 1, line 1 - page 2, line 15; table I, compound no. 17 * ---	1,18,23	TECHNICAL FIELDS SEARCHED (Int. Cl.3)
P,A D	EP-A-0 207 674 (SANKYO CO. LTD.) * page 33, compounds no. 268, 275; claims 1, 29-31 * -----	1,18,19 ,22,23	C 07 D 211/00 C 07 D 401/00 A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	11-01-1988	VAN AMSTERDAM L.J.P.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)